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A STUDY OF THE REISSERT CONDENSATION

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

by

M. VADEKAR

Edmonton, Alberta

May, 1962

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UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and
recommend to the Faculty of Graduate Studies for
acceptance, a thesis entitled

A STUDY OF THE REISSERT CONDENSATION

submitted by M. Vadekar in partial fulfillment of the
requirements for the degree of Doctor of Philosophy.

Date

May 11 / 1962

ABSTRACT

A kinetic study of the Reissert condensation revealed an over-all fourth-order dependence of the rate of condensation on the concentration of the reactants. A kinetic order of one was found for each of o-nitrotoluene and diethyl oxalate, and an apparent kinetic order of two was found for sodium, and potassium ethoxide.

A positive, primary salt effect was observed on the rate of condensation upon the addition of inert salts to the reaction mixture.

The substituent effect was studied in terms of the Hammett equation, and a value of 3.7 was obtained for ρ . This high positive value of ρ indicated that the formation of a carbanion was involved in the rate-determining step or in a step prior to the rate-determining step.

The Reissert condensation was found to be truly reversible in ethanol solvent. When the solvent ethanol was gradually replaced by benzene in a series of reaction runs, the rate of condensation was found to be higher, and the position of the equilibrium was found to be shifted towards higher conversion of the reactants to the product.

An attempt was made to suggest a mechanism to explain the observed characteristics of the reaction.

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INTRODUCTION

A. The Problem

The base-catalyzed condensation of diethyl oxalate with ortho- and para-nitrotoluene was first investigated by Reissert (1) in 1897 to synthesize the corresponding phenylpyruvic acids. On reduction with ammoniacal ferrous sulphate, both the o-nitro-phenylpyruvic acid and p-nitrophenylpyruvic acid were converted to the amino derivatives. However, the ortho isomer immediately cyclized, under these conditions, to indole-2-carboxylic acid, which upon decarboxylation gave indole. Thus the Reissert condensation provided a very convenient method for the synthesis of indole, and various nuclear substituted indoles.

Since the discovery of this reaction, a large number of reports have appeared describing the synthesis of substituted indoles, utilizing the Reissert condensation reaction (7-28). The variable results obtained in condensing a number of substituted o-nitrotoluenes with diethyl oxalate prompted us to study this reaction more closely. It was hoped that the knowledge of the details of this reaction might provide an explanation for the variable results and thus permit the proper choice of conditions which would maximize yields.

Although practical applications of this reaction have been reported quite frequently, there seems to be no account in the literature of any kinetic or mechanistic studies. In view of this, the Reissert condensation reaction was studied kinetically; salt effects, and substituent effects in terms of Hammett sigma-

rho relationship, were determined, and the information thus obtained was examined with a view to proposing an acceptable mechanism for the reaction.

B. Literature Survey

Base-catalyzed condensations of diethyl oxalate have been known for a long time. In such condensations, the second reactant almost invariably is a compound which possesses an active methyl or methylene group. These substances are considered to be very weak acids, the activity or "acidity" of which is attributed to the electron-withdrawing influence of groups attached to the carbon atom of the methyl or methylene group in question. Groups which supply such an activating influence are the cyano, carbonyl (as in a ketone, aldehyde, or carboxylic ester), or a substituted or unsubstituted aromatic ring system (2-5).

For this activating influence to be effective, the electron withdrawing group is either in close vicinity to a methyl or methylene group, or farther removed but connected by a conjugated double bond system. An example of such a transmission of activation through a conjugated double bond system is shown by Lapworth's successful condensation of ethyl crotonate with diethyl oxalate in the presence of sodium ethoxide (5).

Reissert, in 1897, attempted to study the activating influence of the nuclear substituents on the methyl group in toluene. He discovered that diethyl oxalate could be condensed

with o- and p-nitrotoluene in the presence of sodium ethoxide to give ortho- and para-nitrophenylpyruvic acid. Reissert noted that this condensation could be effected only if the nitro group was in the ortho- or para- position to the methyl group. He did not succeed in condensing meta-nitrotoluene and other derivatives of toluene which did not contain a nitro group.

Reissert's original technique of using alcoholic sodium ethoxide as the condensing agent was greatly improved by Wislicenus et al. (6), who introduced the use of potassium ethoxide and also replaced the usual alcohol solvent by anhydrous ether. By this technique, yields of more than 80% of the pyruvate were obtained as against 55% found for Reissert's procedure. In addition to the increased yields, Wislicenus was able to isolate the pyruvic acid as the ethyl ester. Due to the conditions employed in the isolation and purification process, Reissert was able to isolate only the nitrophenylpyruvic acid.

A large number of substituted phenylpyruvic acids have been prepared utilizing the procedure developed by Wislicenus or by Reissert. A number of these are shown in Table I. A wide variety of experimental conditions employed in achieving the condensation is evident on surveying the literature. A review of the results obtained by numerous workers, reveals a certain pattern of the behavior of the substituted toluenes towards condensation.

Snyder and coworkers (19) reported an almost quantitative yield of 5-bromo-2-nitrophenylpyruvic acid using potassium

TABLE I

Substituted Nitrophenylpyruvic Acids Obtained by the Reissert
Condensation

Position of the Substituent in Toluene					Reference
2	3	4	5	6	
NO ₂					1
		NO ₂			1
NO ₂		OMe			8
NO ₂				OMe	9
NO ₂			OMe		9
NO ₂		COOEt			10
NO ₂		CN			10
NO ₂		OMe	OMe		11
NO ₂		OCH ₂ Ph			12
NO ₂			OCH ₂ Ph		16
NO ₂			Br		19
NO ₂		Me			20
NO ₂		Br			22
NO ₂				Br	22
NO ₂				Cl	21
NO ₂		Cl			23
NO ₂	Cl				24
NO ₂				Me	27
NO ₂	Br				28
NO ₂	SCH ₂ Ph				29
NO ₂		SCH ₂ Ph			29
NO ₂				SCH ₂ Ph	29
NO ₂				I	25

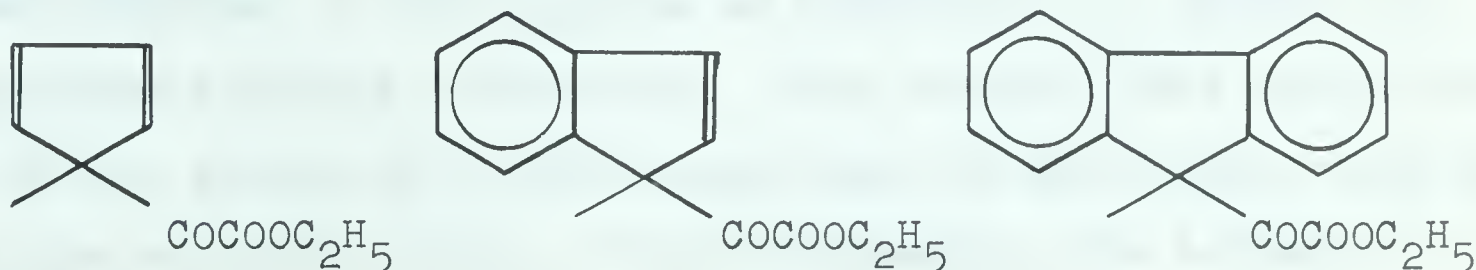
ethoxide in ether as condensing agent. On the other hand, Blaikie and Perkin (9) found that 6-methoxy- and 3-methoxy-2-nitrotoluenes failed to condense in the presence of sodium ethoxide, in alcohol solvent. Similar results have been obtained by Burton and Stoves (12) who found that 4-benzyloxy-2-nitrotoluene did not condense satisfactorily with ethyl oxalate in the presence of sodium ethoxide in an ethanolic medium, but if the potassium ethoxide was employed as condensing agent and ether was the solvent, a 40% yield of the desired product was obtained. Oxford and Raper (11) also experienced the same difficulty in condensing 6-nitrohomoveratrol with sodium ethoxide, but could get 40% yield in potassium ethoxide-ether medium.

It has been generally observed that electron releasing substituents in the aromatic nucleus of o-nitrotoluene retard the condensation reaction, whereas substituents which are moderately electron attracting, such as the halogens, the carboxylic acid group or the ester group, give a very satisfactory reaction with excellent yields under similar conditions.

The compounds 2,4-dinitrotoluene and 4-cyano-2-nitrotoluene were found not to condense satisfactorily (10). In attempts to effect reaction between these compounds and ethyl oxalate, it was observed that the addition of solutions of these compounds in ethanol or ether to a mixture of diethyl oxalate and either sodium or potassium ethoxide in ethanol at room temperature led to the development of a blue colour, but no phenylpyruvate

could be isolated in appreciable quantities. This was confirmed by observations in this laboratory that, 2,4-dinitrotoluene, when treated in the above manner in concentrated solutions (approximately 0.3 M with respect to each reactant) gave the blue colour which disappeared after a short time, and the solution became black and tarry instead of deep red as in a normal reaction. No phenylpyruvate could be isolated. Furthermore, a considerable amount of heat was evolved during these changes, a condition not found in any other nitrotoluene condensation. Kermack (10) did succeed in condensing 4-cyano-2-nitrotoluene in 80% yield by adding an ethanolic solution of it dropwise to a cold mixture of sodium ethoxide and diethyl oxalate, when the blue colour persisted only for a short time and deep red crystals separated. Apparently Kermack did not succeed in condensing 2,4-dinitrotoluene since he reported only the appearance of blue colour when the dinitro compound was mixed with sodium ethoxide and ethyl oxalate.

Thiele (4) has successfully condensed cyclopentadiene, indene, and fluorene with diethyl oxalate in the presence of sodium ethoxide to obtain the corresponding oxalyl derivatives shown below.



Toluene itself has resisted condensation with diethyl oxalate under all conditions employed. These facts agree with the relative acidity of the methyl or methylene hydrogens in these compounds. These reactions show that the electron system of the aromatic ring does enhance the reactivity of the methyl or methylene groups. However, the methylene group in o-nitroethylbenzene failed to condense in spite of the added activating influence of the nitro group. Hardegger and Corrodi (25) attributed the failure of this compound to react with ethyl oxalate to steric hindrance due to the adjacent methyl group. But Uhle (26) has been successful in condensing o-nitrotetralin with ethyl oxalate by the use of a base as powerful as potassium tertiary-butoxide. Furthermore, other sterically hindered derivatives of 2-nitrotoluene have been condensed without much difficulty, examples of which are 6-iodo- (25), 6-methyl- and 6-chloro- (27), 6-methoxy- (9), 6-bromo-, 3-bromo-, 3- and 6-benzylthiotoluene (29). Hence it is likely that an important factor in the failure of 2-nitroethylbenzene to react is the electron-donating effect of the methyl group in the ethyl substituent (36).

Chardonnens and Kramer (32) have studied the condensation of substituted m-xylenes with benzaldehyde and p-dimethylaminobenzaldehyde, in the presence of piperidine, to obtain the corresponding stilbene derivatives. They observed that activation of the methyl groups by a nitro substituent is much higher than by groups such as cyano, alkyl, or aryl sulphonyl in the benzene nucleus.

Along with the normal reaction of p-nitrotoluene with diethyl oxalate in the presence of ethereal potassium ethoxide, a side reaction has been observed (6) in which small quantities of 4,4'-dinitrobibenzyl and 4,4'-dinitrostilbene are formed. Reissert (1) also isolated very small quantities of these bimolecular condensation products from the reaction of o-nitrotoluene with diethyl oxalate in the presence of sodium ethoxide when the concentrations of the reactants were high, e.g., o-nitrotoluene and NaOEt, both one molar and diethyl oxalate, 0.5 molar in dry ether as solvent. Both Reissert (1) and Wislicenus (6) failed to mention any quantitative yields of these binuclear oxidative condensation products.

Tsurata and coworkers (30) have studied the kinetics of the oxidative condensation of p-nitrotoluene in methanolic potassium hydroxide. Stansbury and Proops (31) have reported the same reaction to take place with better yields using some ethers and amines as accelerators. Furthermore, they report that under these conditions, the difficultly condensible o-nitrotoluene reacts to give 36% yield of 2,2'-dinitrobibenzyl.

The necessity of a strong base as a catalyst to induce the reaction of the pseudo acid like nitrotoluene, along with the fact that the product, ethyl nitrophenylpyruvate decomposes to the original reactants in the presence of a base, as shown by Reissert (1) and corroborated in the present work, indicate that this reaction exhibits similar features to those of the Claisen

condensation. In his extensive discussion of the mechanism of the Claisen condensation, Ingold (33) noted the fact that, although there is no kinetic evidence for the reaction, all other evidence available points to a reversible reaction involving a carbanion formation in the rate-determining step.

Lack of kinetic evidence for the Claisen as well as the Reissert condensation reactions may be attributed to the difficulty encountered in finding a suitable analytical procedure to follow the course of the reaction.

RESULTS AND DISCUSSION

A. Analytical Method

In order to study the reaction kinetically, it was necessary to develop an analytical procedure to follow the course of the reaction either by observing the rate of disappearance of the reactants or the rate of formation of the products.

Methods based on analysis of unchanged reactants were found to be unsuitable. No quick and reliable method was available in the literature for the measurement of the concentration of o-nitrotoluene. Infra-red absorption of the original nitro group in the toluene and that in the nitrophenylpyruvate showed no clear cut means of their quantitative separation. Ultra-violet absorption spectra of nitrotoluene also did not show any characteristic absorption peaks which could be clearly distinguished from those of the product nitrophenylpyruvate, and thus be suitable for analysis.

Estimation of diethyl oxalate was also difficult. Generally, oxalic acid can be estimated with good accuracy by converting it to its calcium salt which can then be washed free of any impurity and estimated by permanganimetric titration. There thus existed the possibility that the reaction aliquot could be treated so as to hydrolyze the unreacted oxalate to oxalic acid followed by analysis as indicated above. Consequently, both acidic and basic aqueous hydrolyses were investigated.

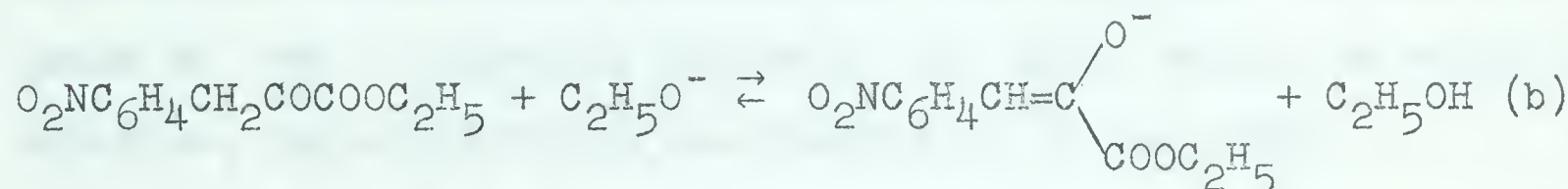
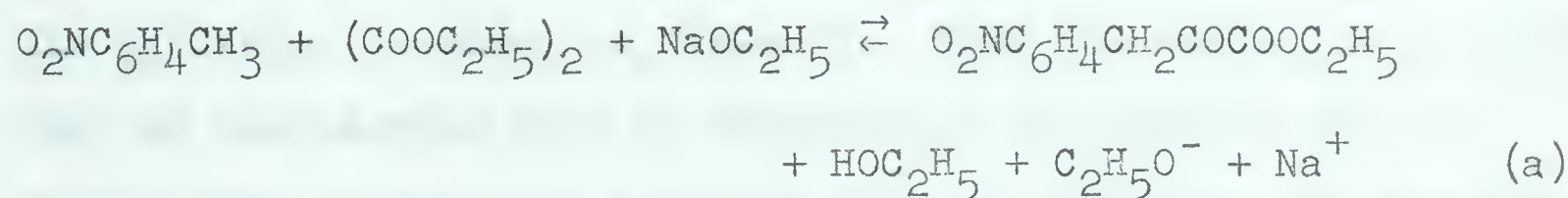
In aqueous or nonaqueous basic solutions, nitrophenylpyruvic acid and its esters are known to decompose to nitrotoluene

and oxalate (1, 29). Hence the basic hydrolysis of the aliquot gave an estimate of the total amount of the oxalate rather than the unreacted portion. Obviously basic hydrolysis was not a suitable analytical method. Since both Reissert (1) and Wislicenus (6) have reported that nitrophenylpyruvic acid is more resistant to acidic hydrolysis than is ethyl oxalate, it was thought that the unreacted ethyl oxalate in the aliquot could be converted selectively to oxalic acid and then to its calcium salt. However, in actual fact, it was found that the phenylpyruvic acid precipitated along with calcium oxalate and no suitable procedure could be found to separate the two quantitatively. For the above reasons, both acidic and basic hydrolyses as a means of following the reaction had to be abandoned.

Analyses based on the Infra-red and Ultra-violet spectrophotometric measurements of the intensity of the carbonyl peaks in diethyl oxalate were also useless, since in the product there was found to exist an equilibrium between the ethyl nitrophenylpyruvate and its enolate and it was found on further investigation, as will be shown later, that the position of this equilibrium depended upon the relative concentrations of the phenylpyruvate and the base in the solution. In addition, there could be found no clear distinction between the carbonyl peaks of the pyruvate and the ethyl oxalate.

Attempts to follow the reaction by analysis of the base employed as the condensing agent proved quite fruitless. In the process of condensation, one molecule of the base eliminated a

molecule of ethanol and also another of ethoxide. Thus the base was regenerated as the reaction proceeded. But part of this regenerated base was used up in establishing the aforementioned equilibrium between the keto-ester and the enol-ester (equations a and b):



The position of the equilibrium in the second step will obviously depend upon the relative concentrations of the keto-ester and the base. Titration of an aliquot from the reaction mixture with a strong acid would always give the total amount of the ethoxide rather than the unreacted base.

Analysis of the product, the nitrophenylpyruvate, proved to be much more useful as a means of following the reaction. A well-known feature of the Reissert condensation is that the product, an α -keto ester, immediately enolizes in the presence of excess base yielding a deep red solution. This characteristic colour of the enolate ion has a sharp absorption in the range of 455-460 $\text{m}\mu$ with λ_{max} at approximately 458 $\text{m}\mu$. Accordingly, an attempt was made to determine whether absorption of the enolate ion could be used to estimate its concentration. Ethyl esters of the o-

and p-nitrophenylpyruvic acids absorbed sharply in the range of 455-460 $m\mu$ with $\lambda_{\max}$ at approximately 458 $m\mu$ as shown in Figures 1, 2 and 3.

When converted to their sodium or potassium enolates, the intensity of absorption was found to depend upon the relative amounts of the base present in the solution for a given amount of the pyruvate, as shown in Table II. From the table, it is evident that an equilibrium such as represented by equation (b) is established between the pyruvate and the ethoxide. In the presence of $\approx$ four-fold excess of the base, sodium or potassium ethoxide, the equilibrium was completely on the right.

A series of experiments showed that the absorbance of the pyruvates followed Beer's Law. By plotting absorbance at 458 $m\mu$ in units of optical density versus known concentrations of various nitrophenylpyruvates in dry ethanol, as long as the base sodium or potassium ethoxide was in considerable excess, a linear relationship was obtained for each compound over a wide range of concentrations. This is illustrated for three examples in Figure 4.

It was observed that the same molar extinction coefficient was obtained for a given nitrophenylpyruvate no matter what the relative concentrations of the base and the pyruvate were used, as long as the ratio of base to pyruvate was ≥ 4 . Thus the alcoholic solutions of the pyruvate made in 0.05, 0.1 or 0.15 M ethoxide still gave the same extinction coefficient. These observations show that the range of base concentration employed in the analysis

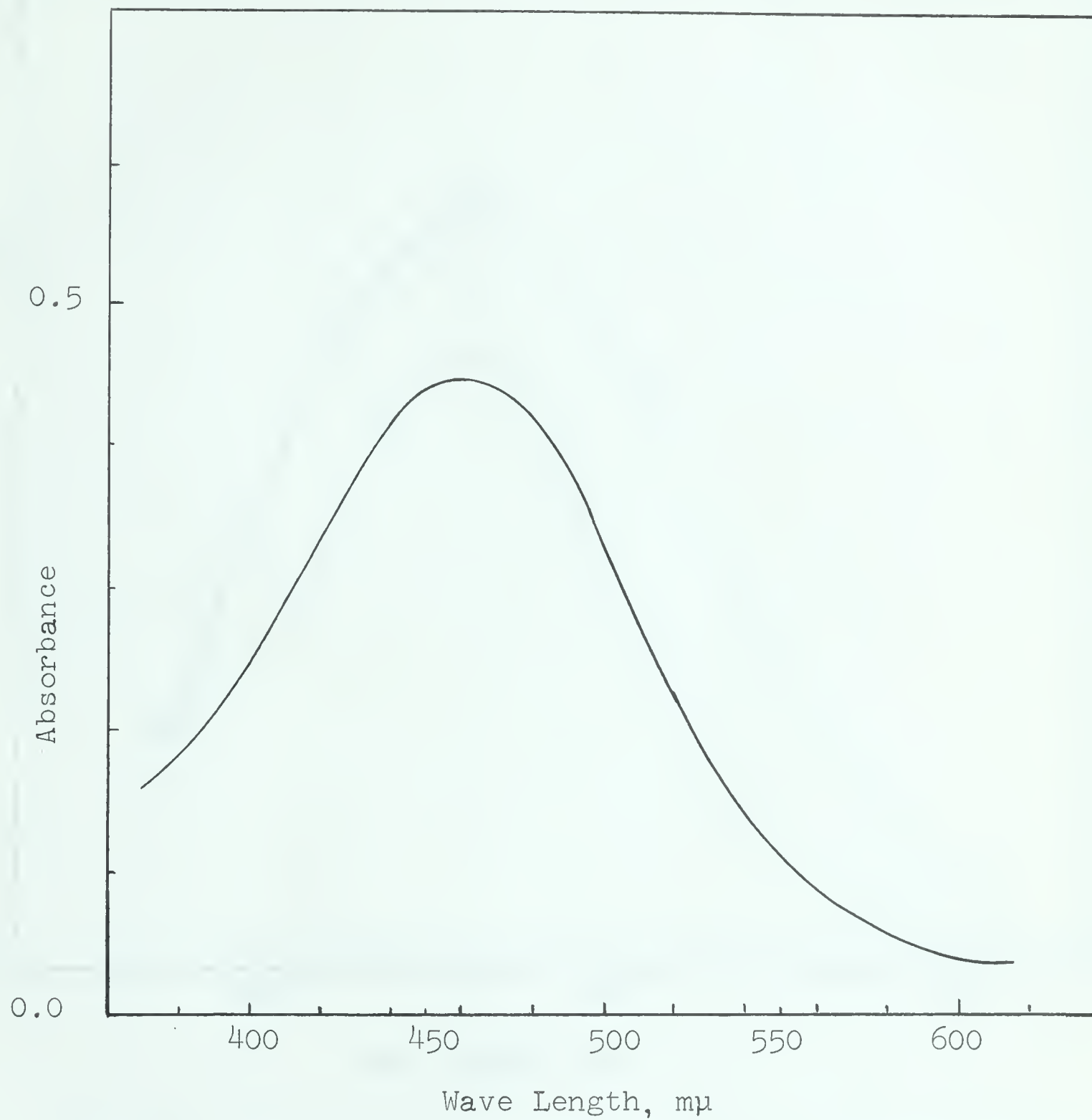


Fig. 1. Absorption spectrum of ethyl 2-nitrophenylpyruvate in anhydrous ethanol 0.1 M in sodium ethoxide.

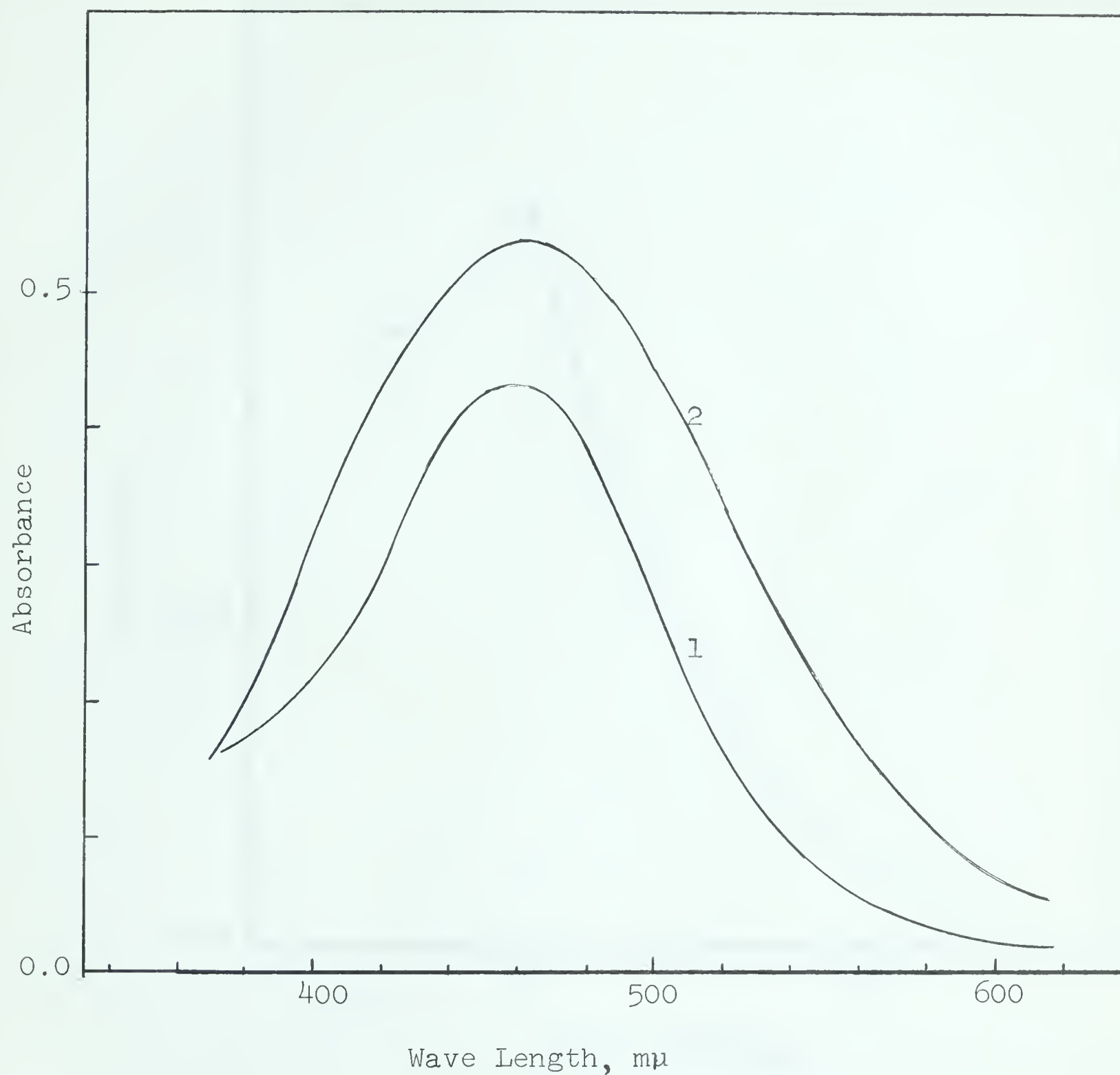


Fig. 2. Absorption spectra of ethyl 4-nitrophenylpyruvate and 4-chloro-2-nitrophenylpyruvate in anhydrous ethanol 0.1 M sodium ethoxide. The plot numbers 1 and 2 refer to 4-nitrophenylpyruvate and 4-chloro-2-nitrophenylpyruvate respectively.

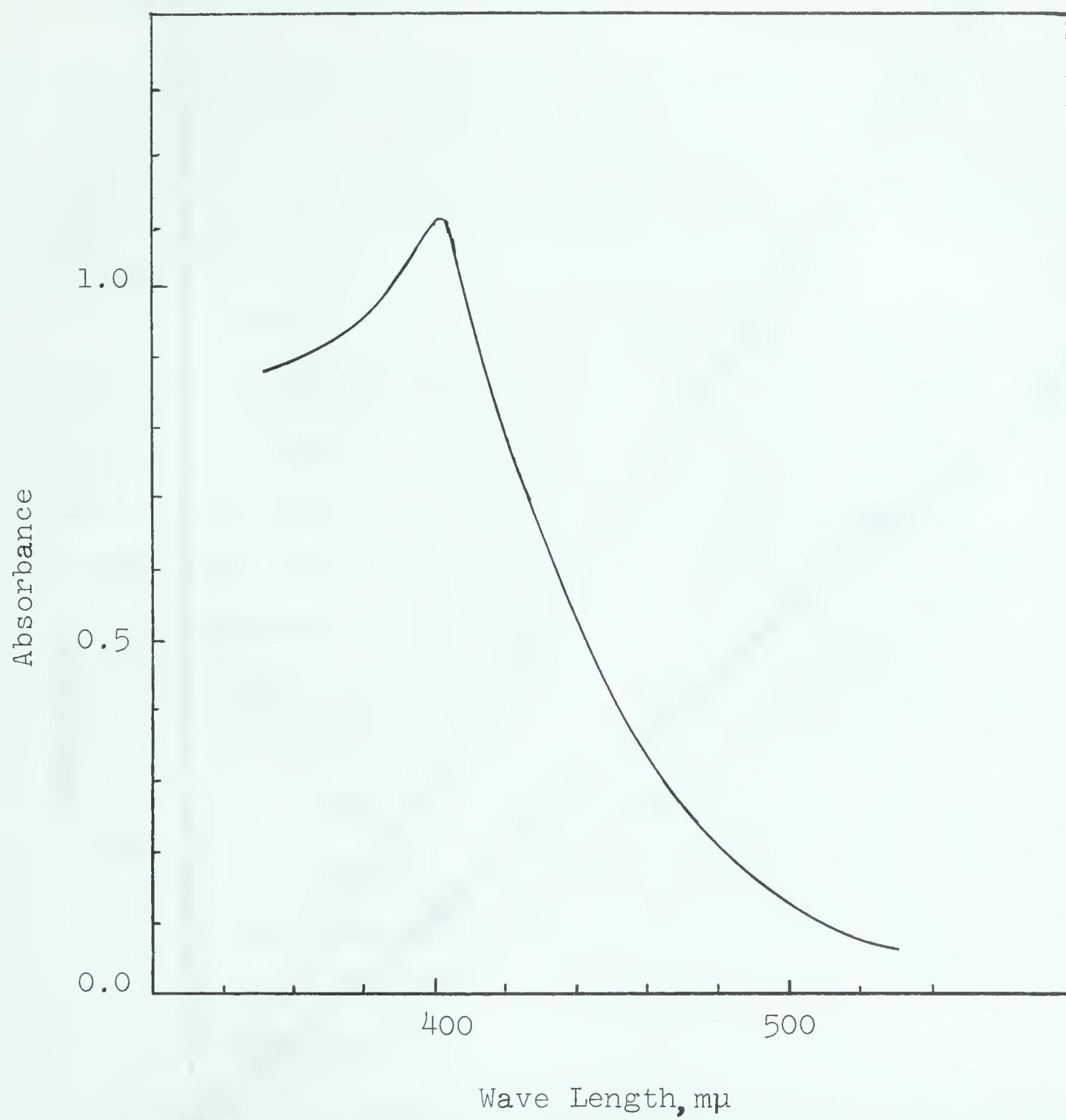


Fig. 3. Absorption spectrum of ethyl 3-bromo-2-nitrophenylpyruvate in anhydrous ethanol 0.1 M in potassium ethoxide.

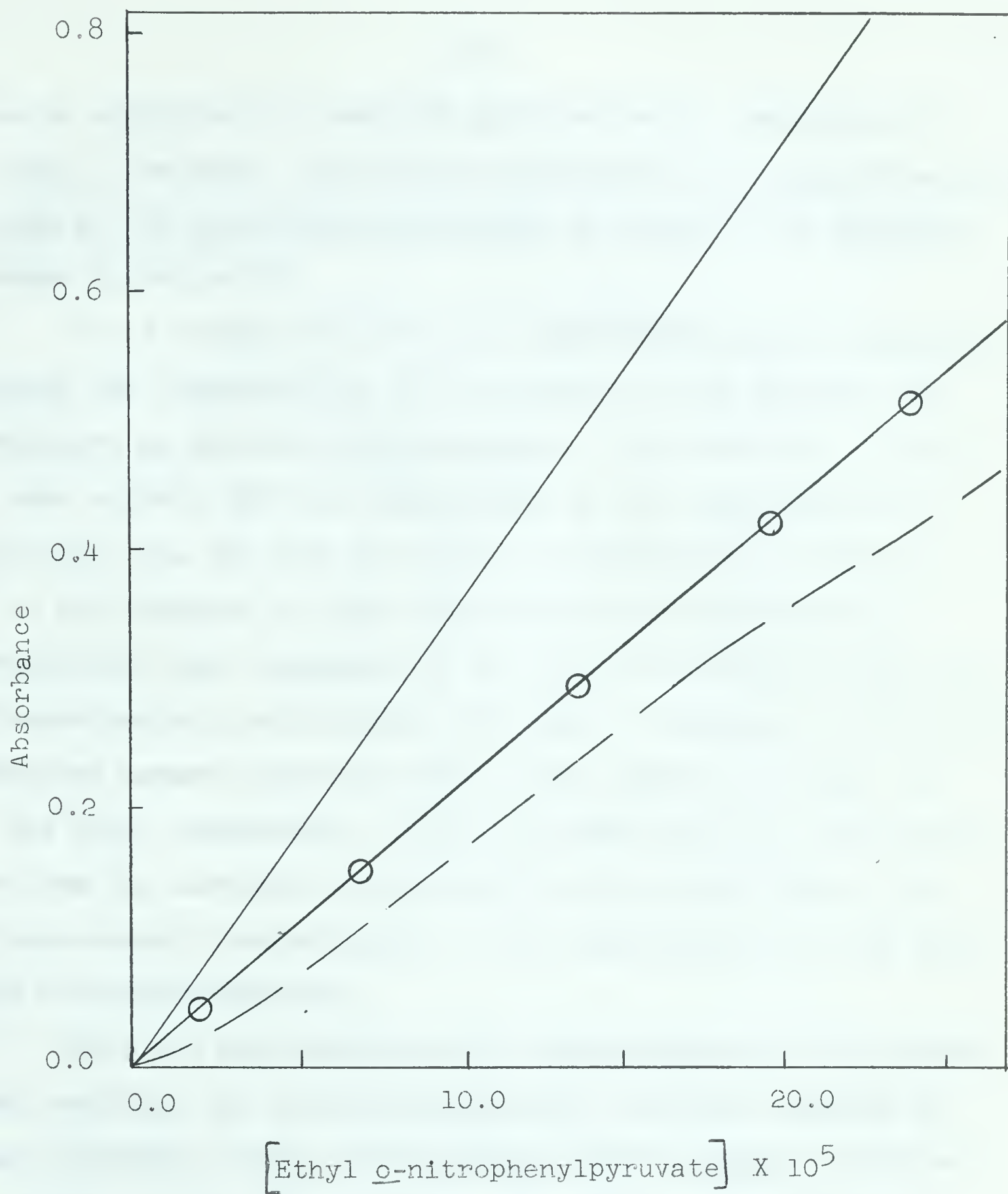


Fig. 4. Beer's Law plot of absorbance at 458 m μ vs. concentration of ethyl *o*-nitrophenylpyruvate in dry ethanol; broken line - for solution containing equimolar proportion of sodium ethoxide, and pyruvate; solid line - for solution containing large excess of sodium ethoxide over the pyruvate, and —○— line for solution of ethyl 4-bromo- and 4-chloro-2-nitrophenylpyruvate containing large excess of sodium ethoxide.

was quite sufficient to move the equilibrium (b) completely to the right. The molar extinction coefficients for a number of substituted o- and p-nitrophenylpyruvates in excess 0.1 M ethoxide are shown in Table III.

It is evident then that the spectrophotometric method of measuring the concentration of the enolate of the pyruvate was satisfactory in following the progress of the reaction. It was then made certain that the measurement of the concentration of the pyruvate via the enol was equally satisfactorily achieved, even in the presence of ethyl oxalate and o-nitrotoluene, by incorporating these compounds in the trial solutions on which the spectrophotometric measurements were made. Extinction coefficients so obtained agreed completely with those reported in Table III. From the above observation, it was concluded that no interference arose from the unreacted ethyl oxalate and nitrotoluene in the spectrophotometric measurements of the concentration of the enol of the nitrophenylpyruvate.

That the spectrophotometric determination of the product of the reaction, the nitrophenylpyruvate, actually measured the product correctly during the reaction, with no change in product concentration during the analysis, was shown by the following tests.

- (a) An aliquot removed from the reaction mixture at 76° was mixed with a large excess (10 times or more of its volume) of 0.1 M ethoxide solution in anhydrous ethanol. This dilution and the

TABLE II

Dependence of the Position of the Keto-Enol Equilibrium of Ethyl
4-Fluoro-2-nitrophenylpyruvate on the Relative Concentration of
 NaOC_2H_5 in Dry Ethanol^{*}

$[\text{Pyruvate}] \times 10^5$ (moles/liter)	$[\text{NaOC}_2\text{H}_5] \times 10^{5**}$ (moles/liter)	Absorbance
13	10	0.054
13	20	0.311
13	30	0.484
13	40	0.490
13	50	0.491
13	910	0.492
13	9100	0.491

* Solutions for the above measurements were made up by diluting 100 λ aliquots of 0.013 M pyruvate and an appropriate amount of 0.01 M (and 0.1 M) NaOC_2H_5 with dry ethanol in a 10 ml. volumetric flask. Measurements were made at 458 m μ on a Beckman Model B Spectrophotometer, in 1 cm. rectangular stoppered quartz cells.

** The actual concentration of the ethoxide may be 20-30% more than the figures indicated.

TABLE III

Extinction Coefficients of Ethyl Nitrophenylpyruvates at 458 m μ ^{*}

Substituent in the Aromatic Ring of Ethyl Phenylpyruvate ^{**}	Base Employed (0.1 M)	Extinction Coefficient x 10 ⁻³ (liter/moles ⁻¹)
2-nitro-	KOC ₂ H ₅	3.70
4-nitro-	"	16.0
4-fluoro-2-nitro-	"	3.91
4-chloro-2-nitro-	"	3.91
4-bromo-2-nitro-	"	4.33
4-iodo-2-nitro	"	4.33
4-methyl-2-nitro	"	3.89
3-bromo-2-nitro-	"	0.457 ^{***}
2-nitro-	NaOC ₂ H ₅	3.72
4-fluoro-2-nitro-	"	3.72
4-chloro-2-nitro-	"	2.21
4-bromo-2-nitro-	"	2.21
4-iodo-2-nitro-	"	2.21

* Measured on a Beckman Model B Spectrophotometer, using 1 cm rectangular stoppered quartz cells.

** Maximum concentration of pyruvate used was 50 x 10⁻⁵ moles/liter

*** λ_{max} was found to be shifted to 400 m μ . Extinction coefficient at 400 m μ was 1.41 x 10³. Beer's law was obeyed at 400 m μ .

consequent decrease of the reaction temperature was quite sufficient to quench the reaction. Since base catalyzes the reaction, an objection could be raised that, although the aliquot was cooled to room temperature, the addition of such a large proportion of base might cause the reaction to continue during the manipulations. It was observed that in reactant concentrations of the order of 0.001 to 0.005 mole per liter or less (a condition occurring in the diluted aliquots) there was no measurable forward reaction at 76° even when the mixture was kept under observation for about 60 minutes. It was clear that there was no significant reaction occurring following the dilution and during the actual measurement of absorbance.

- (b) It is known that solutions of nitrophenylpyruvates in dry alcoholic solutions of ethoxide slowly decompose to ethyl oxalate and nitrotoluene (29). This back reaction might then be significant upon dilution of the aliquot with excess base, and thus the optical absorption measured may be erroneous. It was found that, at room temperature, a 0.0003 M solution of pyruvate in excess of 0.1 M sodium ethoxide decomposed so slowly that during the time the aliquot was removed, diluted and the absorption measured, this reverse reaction was negligibly small. Table IV contains information which illustrates this fact.

In an actual kinetic run, the average time needed to complete the operation of dilution and measurement of absorption on

TABLE IV

Loss of Pyruvate Due to Decomposition by Base

[Ethyl o-nitrophenylpyruvate] = 0.0003 M in 0.1 M NaOC₂H₅.

Solvent, anhydrous ethanol. Reaction temperature, 22°.

Time (in minutes)	Absorbance [*]	% Decomposition
(5-6 seconds)	1.095	0.0
15	1.085	0.92
40	1.050	4.6
85	1.014	7.4
110	0.992	-

* Absorbance was measured in 1 cm rectangular stoppered quartz cells at 458 mμ in a Beckman Model B. Spectrophotometer using ethanol containing 0.1 M NaOC₂H₅ solution as blank.

an aliquot was about 40 to 50 seconds - in any case, less than one minute. Thus, considering the information in Table IV, the loss of pyruvate by solvolysis would amount to considerably less than 1%.

B. Kinetics

Kinetic dependence of the rate of the reaction upon the concentration of each reactant was determined individually by the pseudo-order technique (35). When the concentrations of all the reactants but the one under consideration are at a sufficiently high value so that they remain constant or nearly constant during a run, these concentrations may be included in the experimental rate constant 'k'. In this case the reaction is said to be of 'pseudo-nth order' or 'kinetically of the nth order, with respect to that reactant', where n is the exponent of that concentration which changes during the run. For example, if in the present case the rate expression for the appearance of the nitrophenylpyruvate is given by

$$d(x)/dt = k(a)^n(b)^m(c)^p \quad (c)$$

where x, a, b, c, n, m, and p stand for the pyruvate, nitrotoluene, diethyl oxalate, sodium or potassium ethoxide concentrations and their kinetic orders, respectively, then by keeping the concentrations of, say, ethoxide and diethyl oxalate quite high and that of nitrotoluene relatively very low, the rate expression becomes $\text{Rate} = d(x)/dt = k_n(a)^n$, where

$k_n = k(b)^m(c)^p$. Taking decadic logarithms the equation becomes $\text{Log}(\text{Rate}) = \log(k_n) + n \log(a)$.

From the above equation the value of 'n', the kinetic order of nitrotoluene, can be readily determined by plotting the logarithm of the observed reaction rate versus the logarithm of nitrotoluene concentration when it is varied in such a way that it is always very small in comparison with (b) and (c).

When the kinetic order of a reactant is known, the pseudo-order rate constants for the same can be obtained by the use of the appropriate kinetic expression. For example, the kinetic order of o-nitrotoluene was found to be one. The rate expression for this reactant becomes $\text{Rate} = d(x)/dt = k_1(a-x)$, where a is the initial concentration of the nitrotoluene and x represents the concentration of the nitrophenylpyruvate at time t. On integration of the equation one obtains $k_1 t = 2.303 \log(a-x) + \text{constant}$. If now one plots the time, t, vs $\log(a-x)$, the slopes of the straight lines thus obtained over the range of concentrations studied will give the rate constants.

Similarly the kinetic order and the rate constants for all the reactants can be determined.

In the present case the kinetics of the Reissert condensation reaction was studied by the determination of the initial rates of the reaction, to avoid interference due to the reverse reaction. The study of the reverse reaction and its effect on the extent of the reaction, in terms of per cent

conversion of the starting materials, is presented in a separate section in this report. In the kinetic study reported in the following pages the reactions have been carried to about 4-5% conversion with little interference due to the reverse reaction.

Kinetic Order and Rate Constants of *o*-Nitrotoluene and Diethyl Oxalate

o-Nitrotoluene and diethyl oxalate both showed first-order kinetics. The results of the pseudo-first-order kinetics of both the reactants are presented in Tables V and VI. Rate constants for various concentrations of diethyl oxalate were reasonably good at the higher concentrations of the ester over the range of 0.0309 to 0.124 M. At quite low concentrations of oxalate, however, the value is about half that obtained at the higher concentrations. This peculiar behaviour may, possibly, be due to absorption of moisture from the air in minute amounts. At such low concentrations of the oxalate, minute amounts of water would be important. Introduction of any moisture would hydrolyze the diethyl oxalate to sodium or potassium ethyl oxalate and thus destroy the reacting species. Adickes has shown that such hydrolysis occurs when ether solutions of diethyl oxalate and alkali metal alkoxide are exposed to small amounts of water either by deliberate additions of water or exposure of the mixture to atmospheric moisture. Figures 5 and 6 show the pseudo-first-order plots. The rate constants were calculated by measuring the

TABLE V

Dependence of the Rate of Reissert Condensation upon the Concentration of ortho-Nitrotoluene

[Diethyl oxalate] = 0.376 M. [NaOC₂H₅] = 0.390 M. Ionic strength, 0.390. Solvent, dry ethanol. Reaction temperature, 76.3°.

[<u>o</u> -Nitrotoluene] (M)**	Pseudo-first-order rate constant, $k_1 \times 10^3$ (min ⁻¹)***	% Conversion of nitrotoluene to pyruvate*
0.0083	2.39	11
0.0147	2.58	12
0.0294	2.62	10
0.0588	2.35	9
0.0735	2.56	9

* The per cent conversion figures quoted are only those obtained for the period over which the log(a-x) versus "t" plot gave a straight line. If the solution was left for a sufficiently long time, the per cent conversion was quite high, i.e. 25-30%.

** The pertinent rate data are presented in Table XXII.

*** The rate constants were obtained by measuring the initial slope of the plot of log(a-x) versus time, and multiplying it by 2.303. A sample calculation is shown in Table XXVI and Figure 15.

TABLE VI

Dependence of the Rate of Reissert Condensation on the Concentration of Diethyl Oxalate

[o-Nitrotoluene] = 0.398 M. [NaOC₂H₅] = 0.408 M. Ionic strength, 0.408. Solvent, anhydrous ethyl alcohol. Reaction temperature, 76.3°.

[Diethyl oxalate] (M) **	Pseudo-first-order rate constants, $k_1 \times 10^3$ *** (min ⁻¹)	% Conversion of oxalate to the pyruvate*
0.0085	1.20	5
0.0170	1.00	5
0.0309	1.88	10
0.0450	2.44	11
0.0618	2.42	10
0.0927	2.34	12
0.124	2.65	15

* See footnote of Table V.

** The pertinent rate data is presented in Table XXIII.

*** See footnote of Table V.

initial slopes of the plots of $\log(a-x)$ and $\log(b-x)$ versus time, and multiplying by 2.303. A sample calculation in detail has been shown in Table XXXVI and Figure 15.

Salt Effects

In the determination of the kinetic order with respect to o-nitrotoluene and ethyl oxalate, the ionic strength was considered to be constant during the entire series of runs since the sodium (or potassium) ethoxide, the only ionic species present, was the same concentration in all cases. However, in a study of the dependence of the reaction upon base concentration, addition of inert salts was necessary to keep the ionic strength constant when the concentration of the base was varied. This problem posed some difficulties since in choosing salts for this purpose, it was necessary to select those which were not only inert but were sufficiently soluble in the solvent in which the reaction was carried out. Perchlorates of the alkali metals are usually quite suitable since they are very weak nucleophiles. Lithium perchlorate is quite soluble in alcohol but it could not be used in the present case because, in the presence of the ethoxides of sodium or potassium, the more insoluble perchlorates of sodium or potassium precipitated. A very serious limitation on the search for suitable salts for use in the kinetic study was their solubility in alcohol. In an extensive survey, it was found that the only salts that were sufficiently soluble were

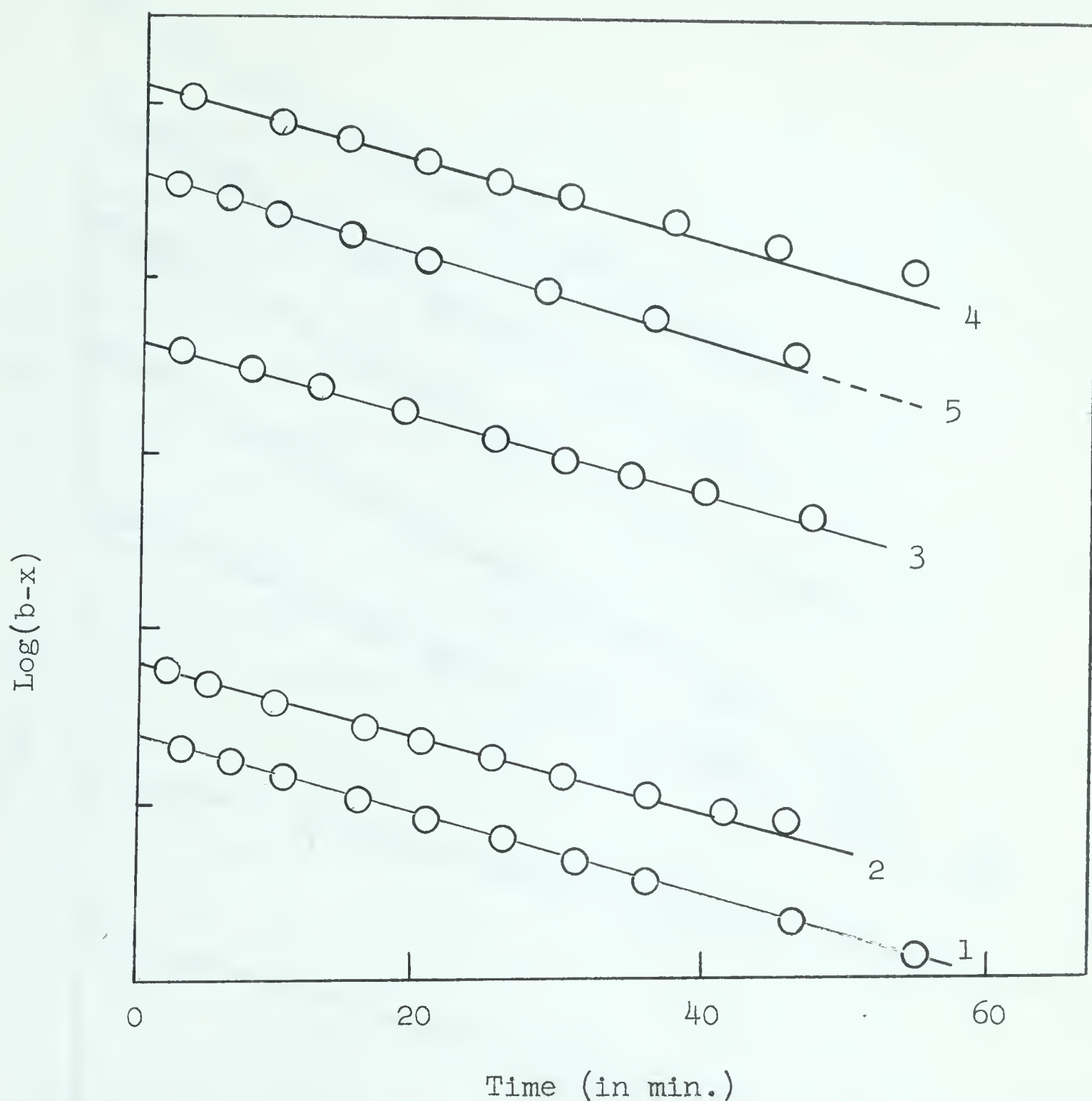


Fig. 5. Typical first-order plots indicating first order-dependence of the rate of condensation on the concentration of *o*-nitrotoluene (ref. Table V). Initial concentration of *o*-nitrotoluene - 0.0147, 0.0588, 0.0735, 0.0083, 0.0294, refer to plots 1 to 5, respectively. The plots are drawn to the same scale but are assembled on one graph for convenient comparison.

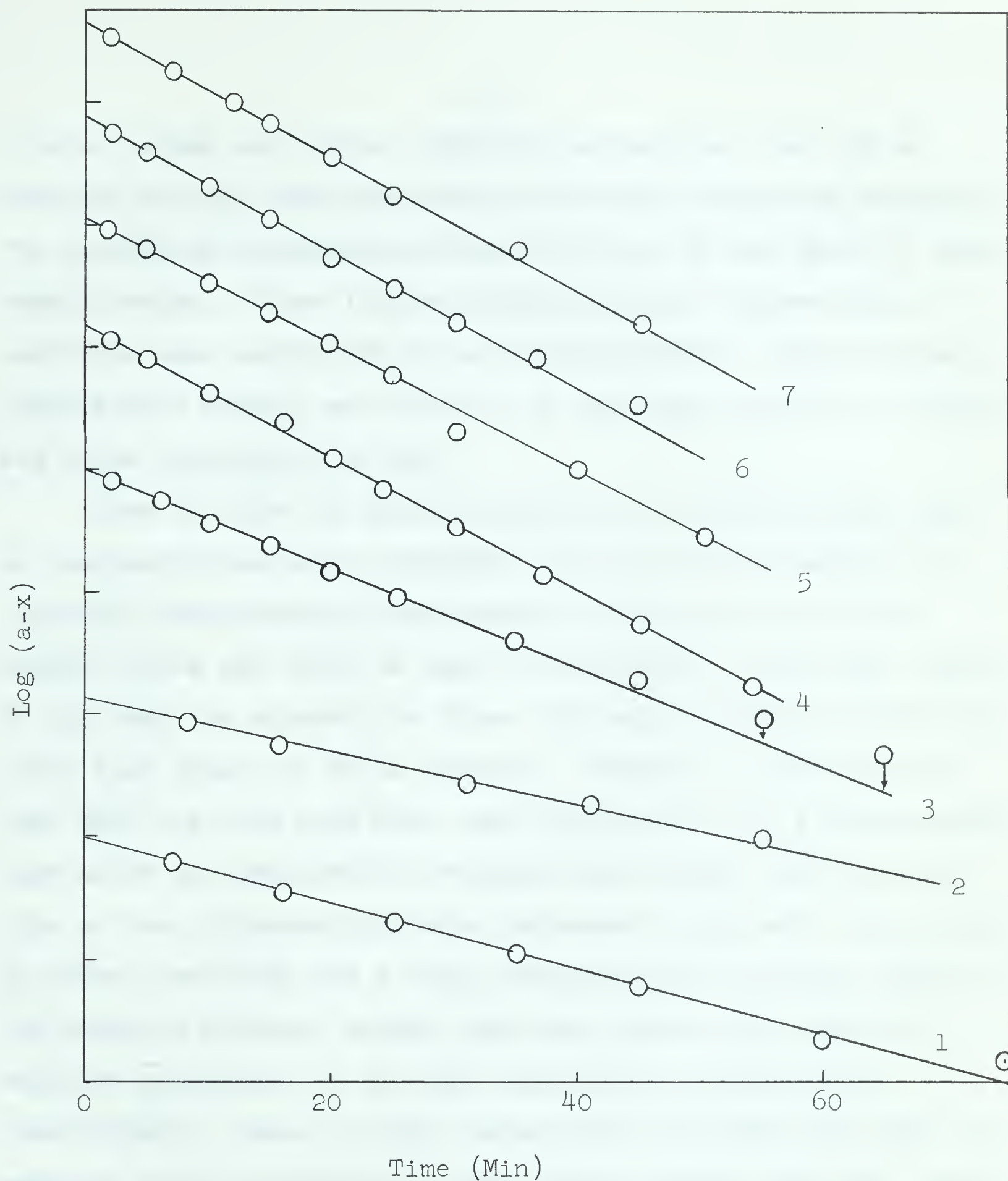


Fig. 6. Typical first-order plots indicating first-order dependence of the rate of condensation on the concentration of diethyl oxalate (ref. Table VI). Initial concentration of diethyl oxalate - 0.0085, 0.0170, 0.0309, 0.0450, 0.0618, 0.0927, 0.124 for plot numbers 1 to 7, respectively. The plots are drawn to the same scale, but assembled on one graph for convenient comparison.

lithium iodide and sodium iodide in conjunction with sodium ethoxide as base, and potassium acetate with potassium ethoxide. The solubility limitation prevented the use of the salts of many organic acids. Since lithium iodide was quite hygroscopic, it was found more convenient to use sodium iodide. Sodium acetate, surprisingly enough, was found to be sparingly soluble in ethanol, and hence unsuitable for use.

From the data in Tables VII and VIII, it can be seen that, on increasing the ionic strength, the rate of the reaction is increased considerably, thus showing a positive salt effect. Sodium iodide was found to show no detrimental effect when added to the reaction mixture for those runs which lasted a relatively short time (about 45 to 50 minutes). However, it was noticed that when the runs were kept under observation for a considerable time after the reaction had reached equilibrium, the concentration of the nitrophenylpyruvate decreased slowly and continuously in those runs which had a large concentration of sodium iodide in the reaction mixture, whereas the ones without any added salt could be maintained at the same equilibrium concentration indefinitely. Hence, it was feared that the iodide ion might be reacting with the product in some unknown manner over the longer time of these runs. For the above reason, the salt effects with respect to sodium iodide were not studied any further. On the other hand, potassium acetate gave very satisfactory results, and runs conducted with this salt showed no evidence of side

TABLE VII

Effect of the Change of Ionic Strength on the Rate of the Reissert
Condensation in the Presence of Sodium Ethoxide *

[o-Nitrotoluene] = 0.376 M. [Diethyl oxalate] = 0.376 M. Salt
added, sodium iodide. Solvent, anhydrous ethanol. Reaction
temperature, 76.3°

[Sodium ethoxide] (M)	[Sodium iodide] (M)	Total ionic strength	Initial rate of con- densation, X 10 ⁵ moles/liter/min.
0.0244	0.000	0.0244	1.67
0.0244	0.502	0.526	2.50
0.0488	0.000	0.0488	5.33
0.0488	0.502	0.551	9.33
0.0732	0.000	0.0732	9.3
0.0732	0.502	0.576	14.3

* The rate data are presented in Table XXIV.

** The rates were obtained by measuring the initial slopes of
the plots of the pyruvate concentration versus time.

TABLE VIII

Effect of the Change of Ionic Strength on the Rate of the Reissert

Condensation in the Presence of Potassium Ethoxide *

[o-Nitrotoluene] = 0.376 M. [Diethyl oxalate] = 0.376 M. Salt added, potassium acetate. Solvent, anhydrous ethanol. Reaction temperature, 76.3°.

[Potassium ethoxide] (M)	[Potassium acetate] (M)	Total ionic strength	Initial rate of condensation, X 10 ⁵ moles/liter/min. ^{**}
0.0472	0.000	0.0472	7.85
0.0472	0.0475	0.0929	8.69
0.0472	0.0914	0.138	9.50
0.0472	0.183	0.230	10.9
0.0472	0.471	0.518	13.6

* The rate data are presented in Table XXV.

** The rates were obtained by measuring the initial slopes of the plots of the pyruvate concentration versus time.

reactions even at high acetate concentrations.

The ion concentrations involved in this work are well above those of the dilute solutions in which the Debye-Hückel equation is valid. For this to be applicable, concentrations of the order of 0.01 M or less are required. Furthermore, the equation is valid for reactions between ionic species in solvents of high dielectric constant (39). The solvent in the present case is ethanol, which has the dielectric constant of the order of 24 at 76°, and one of the reacting species is an electrically neutral molecule. Hence neither the equation $\ln k = \ln k_0 + 2z_A z_B \sqrt{\mu}$ nor $\ln k = \ln k_0 + (b_0 + b_A - b) \mu$ is applicable. However, in a situation like this, the following empirical equation has been used to interpret the observed salt effects (37),

$$k \approx k_0 + \beta_s \mu$$

where k and k_0 are the rate constants with and without added salt, β_s is a constant, and μ is the ionic strength. A similar equation has been used by Winstein and coworkers in their work on the solvolysis of reactions of organic halides in non-polar solvents (40). Using the rate data from Table VIII and the above equation, a plot of initial rates versus ionic strength gives a straight line with a slope of 2.02. Figure 7 shows this plot. The

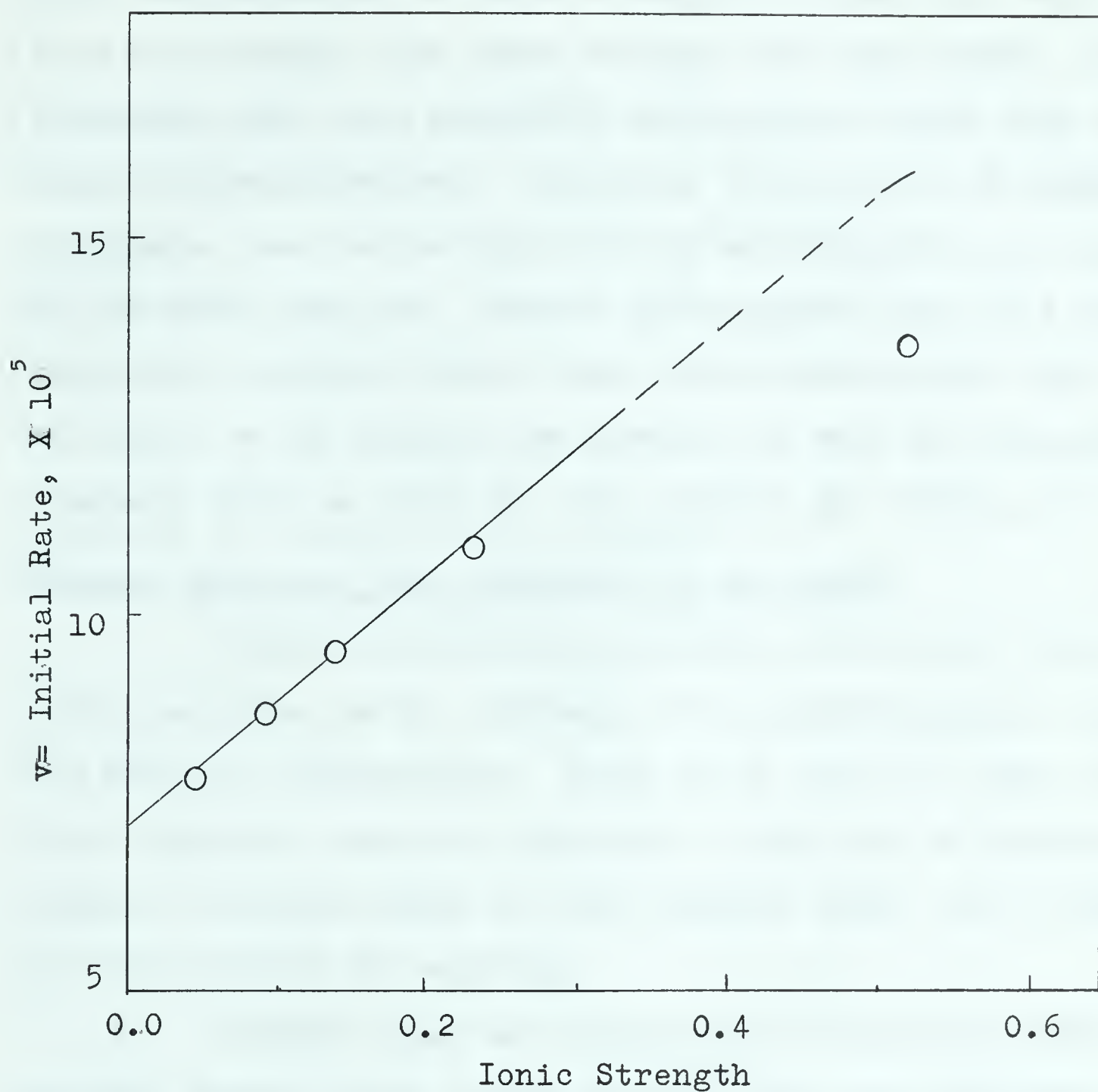


Fig. 7. Primary salt effect on the base-catalyzed condensation of o-nitrotoluene with diethyl oxalate. The rates reported in Table VIII were used for the plot.

point corresponding to ionic strength 0.518 deviates considerably from the straight line drawn through the other points, thus indicating that this empirical relationship breaks down at such high ion concentrations. Formation of ion pairs or higher ion aggregates such as ion triplets may be responsible for the failure of the above equation. Krause (38) reported that in a medium of dielectric constant 35-50, these ionic associations start and ion pairs or ion dipoles are formed, and when the dielectric constant falls to about 20, ion triplets are formed. (The dielectric constant of ethanol at 76° is about 24.)

Kinetic Order and Rate Constants of the Bases

Sodium and potassium ethoxide are the two bases extensively employed in the syntheses of nitrophenylpyruvic acids by the Reissert condensation. Hence it is quite in order to show their relative catalytic influence on the rate of condensation before a detailed study of their kinetic order, rate constants, and salt effects is reported.

Initial rates of condensation of o-nitrotoluene with diethyl oxalate using sodium ethoxide and also potassium ethoxide as a catalyst, under similar conditions, are reported in Table IX. It can be seen that the rates of condensation with potassium ethoxide are higher than those with sodium ethoxide. This result is expected since the former ethoxide is a stronger base than the latter.

The kinetic dependence of the rate of condensation on the concentration of the base was found to be more complex than that for the other two reactants. A plot

TABLE IX

Comparison of Potassium Ethoxide and Sodium Ethoxide as Catalysts
for the Reissert Condensation *

[*o*-Nitrotoluene] = 0.376 M. [Diethyl oxalate] = 0.376 M. Ionic strength $\approx$ 0.048.** Solvent, anhydrous ethanol. Reaction temperature, 76.3°.

Base used	Concentration of the base (M)	***
		Initial rate of condensation, $\times 10^5$ (moles/liter/min.)
Sodium ethoxide	0.0488	5.33
Potassium ethoxide	0.0472	7.84

* The rate data are presented in Tables XXIV and XXV.

** Ionic strength 0.048 is an average of the base concentrations used.

*** The rates were obtained by measuring the initial slopes of the plots of the pyruvate concentration versus time.

of $\log(\text{rate})$ versus $\log[\text{base}]$ was made and it was found that the slope of the best straight line obtained for potassium ethoxide was 1.9, thus indicating a probable kinetic order of 2 with respect to this base. Similar treatment for runs with sodium ethoxide as base gave a slope of 2.2. Figure 8 shows these two plots.

The rate constants were obtained by using the second-order kinetic expression. Results with potassium ethoxide and sodium ethoxide are presented in Tables X and XI, respectively. The second-order plots for potassium ethoxide are shown in Figure 9.

The information accumulated thus far indicates that the over-all kinetics of the reaction is of the fourth order, at least in the range of concentrations studied. In order to verify this conclusion, taking all three reactants in equimolar concentrations, fourth-order rate constants were determined for a limited range of concentrations. Limitations were imposed on concentrations available for study since concentrations higher than 0.5 M led to precipitation of the product (enolate) at about 27-30% conversion, and concentrations lower than 0.03 M led to less than 0.2% conversion even when the reaction mixture was kept under observation for 300 minutes. Table XII shows the relation of the per cent conversion to initial reactant concentration, and the equilibrium constants.

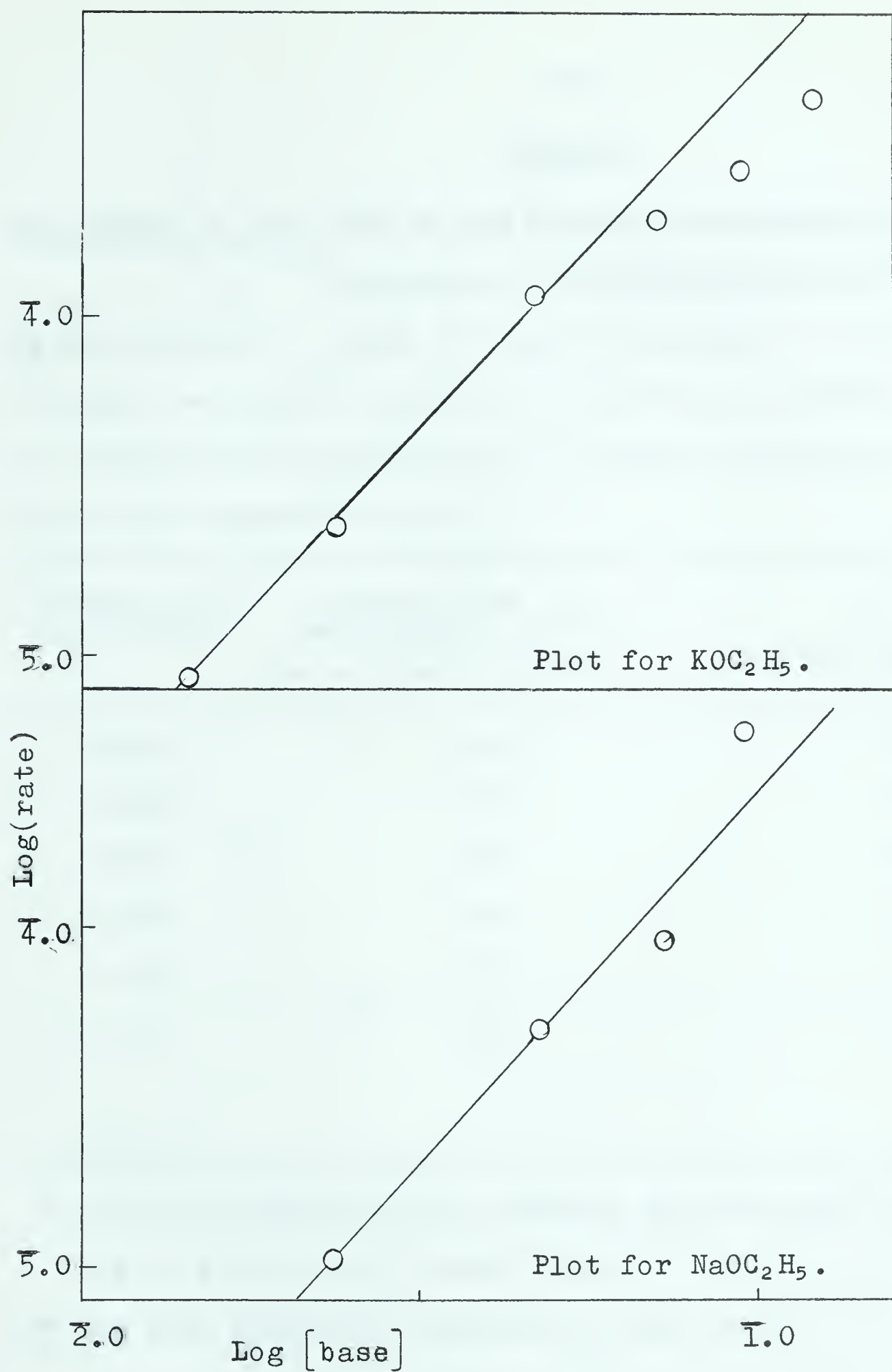


Fig. 8. Plot of $\log[\text{base}]$ vs. $\log(\text{rate})$ to determine the kinetic order of base in the Reissert condensation. The rates reported in Tables X and XI were used for the plot.

TABLE X

Dependence of the Rate of the Reissert Condensation on the Con-
centration of Potassium Ethoxide **

[o-Nitrotoluene] = 0.376 M. [Diethyl oxalate] = 0.376 M. Ionic strength maintained constant at 0.279 by appropriate additions of potassium acetate solution. Solvent, anhydrous ethanol. Reaction temperature, 76.3°.

[Potassium ethoxide]	Initial rate of condensation, $\times 10^4$ (mole liter ⁻¹ min ⁻¹)	$k_2 \times 10^2 *$ (liter mole ⁻¹ min ⁻¹)
0.0142	0.093	4.86
0.0236	0.243	4.85
0.0471	1.06	4.84
0.0707	1.90	4.64
0.0943	2.72	3.33
0.118	4.38	3.11

* The rate constants were obtained by measuring the slope of the plot of $1/(c-x)$ versus time.

** The rate data are presented in Table XXVI.

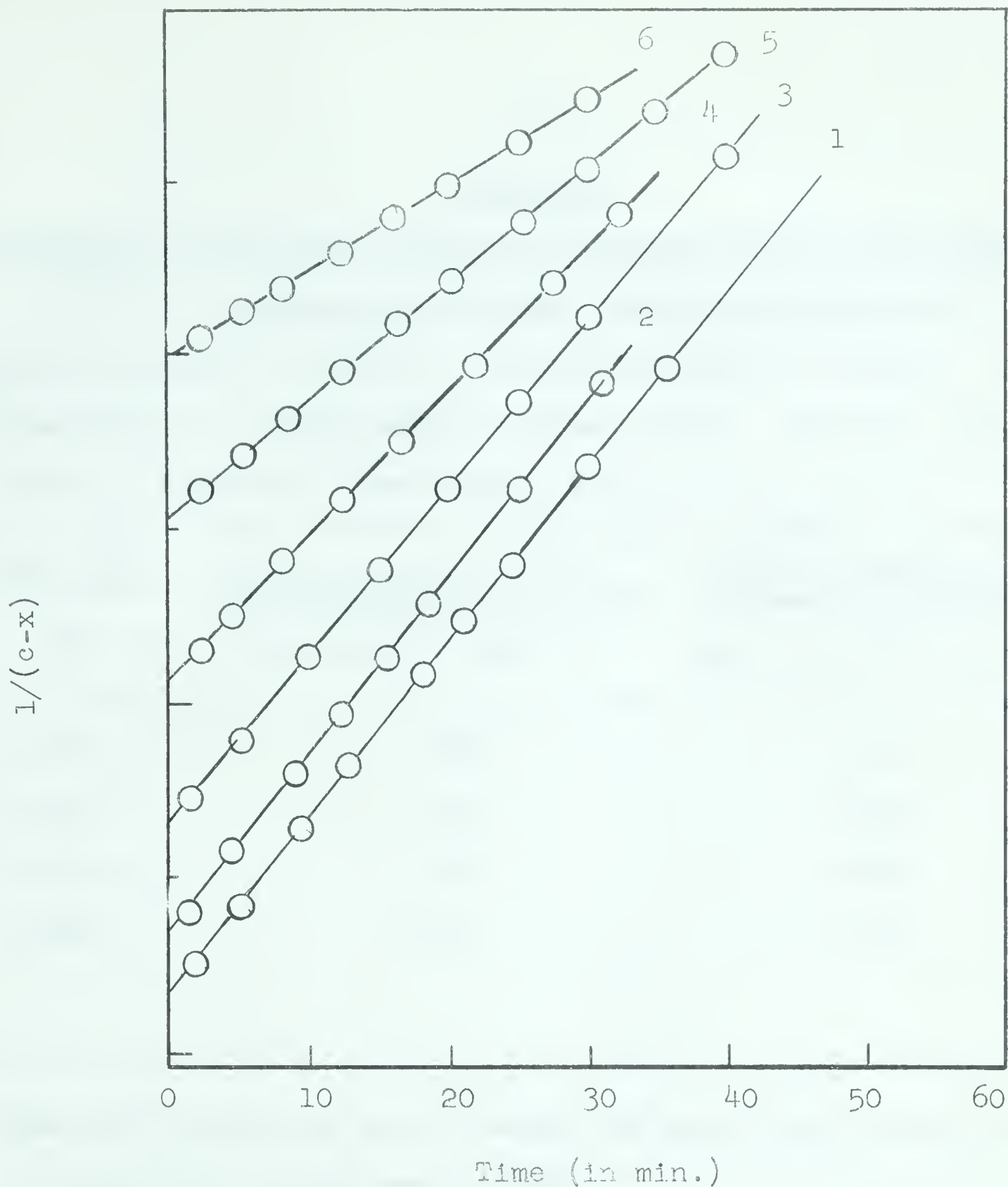


Fig. 9. Typical plots indicating second-order dependence of the rate of condensation on base concentration in the base-catalyzed condensation of *o*-nitrotoluene with diethyl oxalate (ref. Table X). Plot numbers 1 to 6 refer to potassium ethoxide concentrations 0.0471, 0.0236, 0.0142, 0.0707, 0.0943, 0.118 M, respectively. Plots are drawn to the same scale on the $1/(c-x)$ axis, but are assembled on one graph for convenient comparison.

TABLE XI

Dependence of the Rate of Reissert Condensation on the Concentration of the Base, Sodium Ethoxide **

[o-Nitrotoluene] = 0.376 M. [Diethyl oxalate] = 0.376 M. Ionic strength, 0.15. Salt added, sodium iodide. Solvent, anhydrous ethanol. Reaction temperature, 76.3°.

[NaOC ₂ H ₅] (M)	Pseudo-second-order rate constant, $k_2 \times 10^{2*}$ (liter mole ⁻¹ min ⁻¹)	Initial rate of condensation, $\times 10^4$ (mole liter ⁻¹ min ⁻¹)
0.0236	1.82	0.105
0.0473	2.20	0.504
0.0710	1.86	0.920
0.0944	2.01	2.15

* The rate constants were obtained by measuring the slope of the plot of $1/(c-x)$ versus time.

** The pertinent rate data are presented in Table XXVII.

*** Initial rates were obtained as mentioned before.

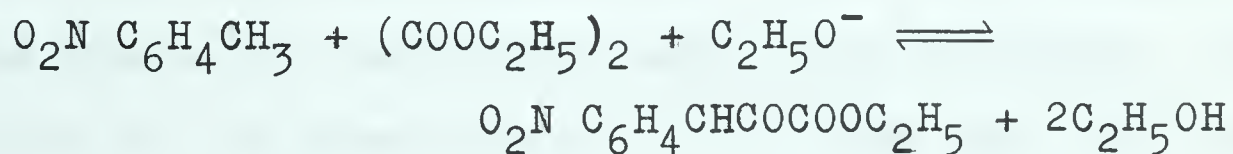
TABLE XII

Effect of the Relative Amount of the Solvent to the Reactants
on the Per Cent Conversion of Reactants to the Product

[o-Nitrotoluene] = [Ethyl oxalate] = [NaOC₂H₅] = [R]. Solvent,
 dry ethanol. Reaction temperature, 76.3°.

[R] (M)	Equilibrium constant* (liters ² moles ⁻²)	% conversion at equilibrium
0.0320	1.96	0.2
0.0490	4.28	1
0.0946	5.23	2
0.110	2.23	3
0.130	3.76	5
0.175	3.07	9
0.180	3.68	9
0.336	** --	--
0.522	** --	--

* Equilibrium constants were calculated using the over-all equation



** In these cases, the equilibrium constant could not be found since precipitation of the enolate of the pyruvate occurred before the equilibrium was established.

The over-all fourth-order rate constants were obtained from the slopes of the plots of $1/(c-x)^3$ vs time, using the initial portion of the reaction where these plots were linear and the reverse reaction was insignificant. To illustrate the negligible effect of the reverse reaction on the initial rates and hence the rate constants, a complete fourth-order plot up to the equilibrium point has been shown in Figure 16. The results of this series of runs are reported in Table XIII and the fourth-order plots in Figures 10 and 11. It is to be noted that the ionic strength was not maintained constant in this series since it was found that addition of inorganic salts to the reaction mixtures with reactant concentrations of 0.2 M or higher caused the product to precipitate very early in the reaction. Thus the ionic strength increased with the reactant concentration (since equimolar concentrations were used). This would be expected to cause an upward drift in the rate constants with increasing ionic strength. Surprisingly enough, this was not found to be the case.

C. Substituent Effect

It was observed in a qualitative study of the condensation of various 2-nitrotoluene derivatives that, under comparable conditions, the yields of the product were quite different, depending on the nature of the substituent. It is found that the reactivity of the methyl group is mainly due to the presence of the nitro group in the aromatic ring. Furthermore, Reissert mentioned that for sufficient activation of the methyl group to cause the condensation with ethyl oxalate, not only was the presence of the nitro group in the ring essential, but also the nitro group had to be in

TABLE XIII

Over-all Fourth-Order Dependence of the Rate of the Reissert
Condensation on the Concentrations of o-Nitrotoluene, Diethyl
Oxalate, and Ethoxide*

$[\text{o-Nitrotoluene}] = [\text{Diethyl oxalate}] = [\text{Base}] = [R]$. Solvent,
dry ethanol. Reaction temperature, 76.3°

Base used	$\frac{[R]}{(M)}$	Fourth-order rate constant, $\times 10^{***}$ (liter ³ mole ⁻³ min ⁻¹)
NaOC ₂ H ₅	0.285	0.577
	0.336	0.577
	0.409	0.507
	0.522	0.577
KOC ₂ H ₅	0.107	1.24
	0.131	1.18
	0.179	1.11
	0.362	1.12
	0.522	0.933 ^{**}

* For the pertinent rate data, see Tables XXVIII and XXIX.

All the rates were measured over a period of 10-12% conversion
of the reactants to the products.

** Product precipitation occurred at a very early stage.

*** The fourth order rate constants were obtained by dividing the
slope of the plot of $1/(a-x)^3$ versus time by 3.

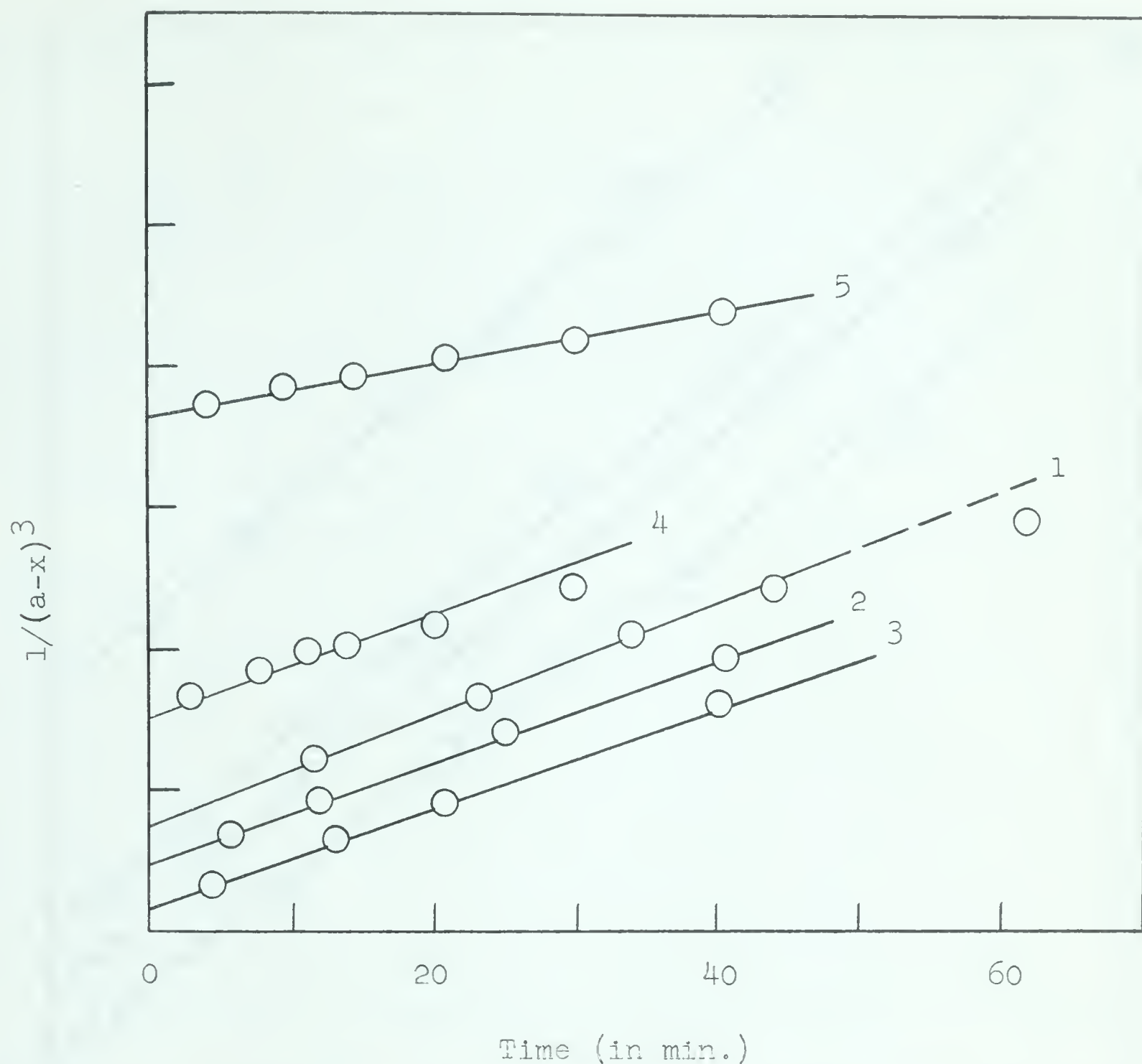


Fig. 10. Typical fourth-order plots indicating an over-all fourth-order kinetics of the condensation of *o*-nitrotoluene with diethyl oxalate in the presence of potassium ethoxide. Concentrations of the three reactants are equimolar in a given run. Plot numbers 1 to 5 refer to reactant concentrations - 0.107, 0.131, 0.179, 0.362 and 0.522 M, respectively (ref. Table XIII). The plots are drawn to the same scale, but are assembled on one graph for convenient comparison. A sample calculation in detail is shown in Table XXXVII and Figure 16.

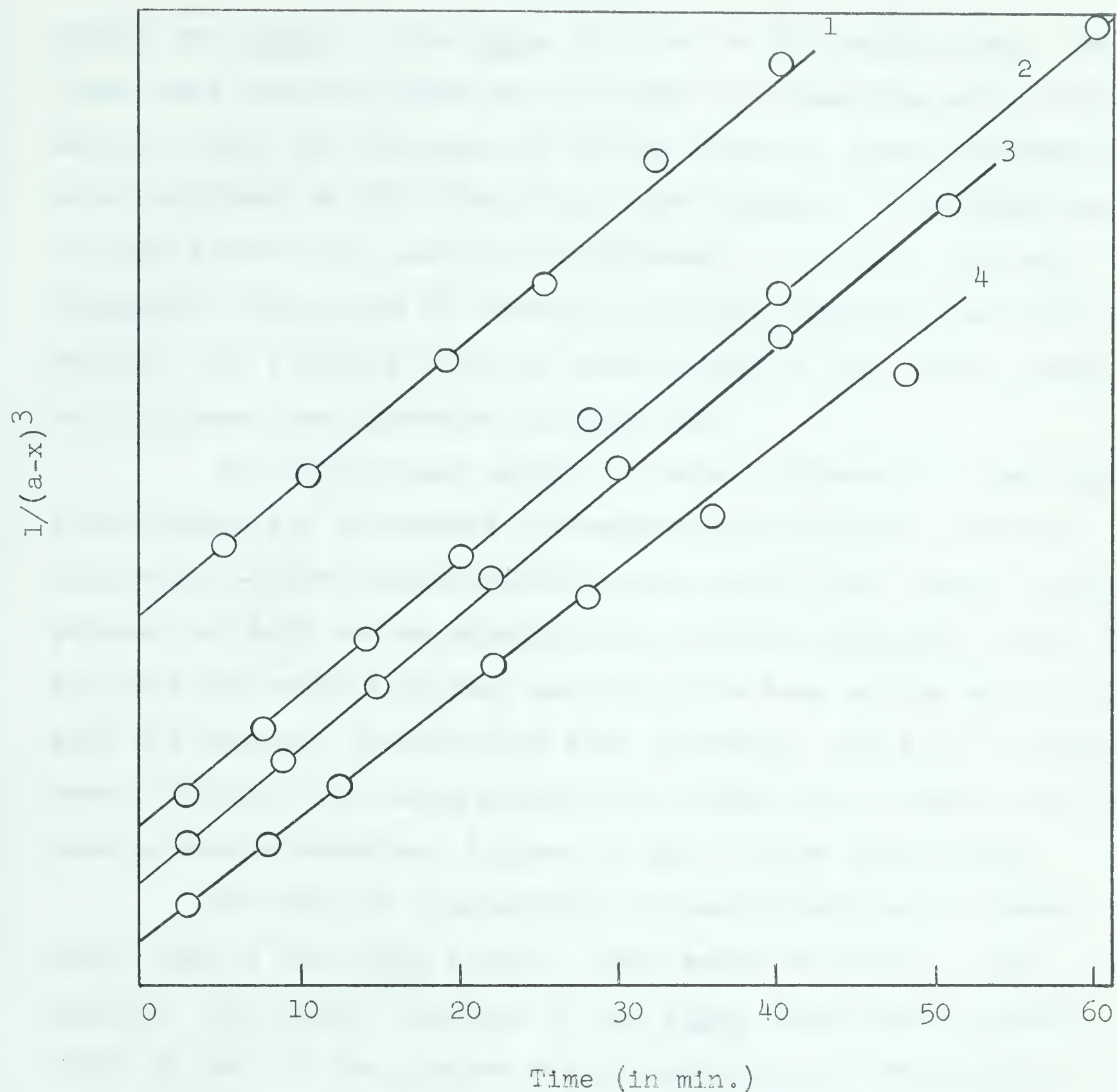


Fig. 11. Typical fourth-order plots indicating over-all fourth-order kinetics of the condensation of *o*-nitrotoluene with ethyl oxalate in the presence of sodium ethoxide. Concentrations of the three reactants are equimolar in a given run. Plot numbers 1 to 4 refer to reactant concentrations 0.285, 0.522, 0.336 and 0.409 M, respectively (ref. Table XIII). The plots are drawn to the same scale, but the lines are assembled on one graph for convenient comparison.

either the ortho- or the para- position to the methyl group. He found that 3-nitrotoluene was incapable of condensing with ethyl oxalate under the influence of sodium ethoxide. These observations were confirmed in this laboratory where attempts to condense the toluene derivatives mentioned by Reissert, even using the more favourable conditions of ethereal potassium ethoxide, met with no success. The relative rates of condensation of the three isomeric nitrotoluenes are presented in Table XIV.

The substituent effect in terms of Hammett's sigma-rho relationship was determined by comparing the reaction rates of different 4-substituted-2-nitrotoluenes with ethyl oxalate in the presence of both sodium ethoxide and potassium ethoxide. Table XV includes the results of runs employing the base sodium ethoxide and also the over-all fourth-order rate constants. Table XVI contains results obtained by using pseudo-first-order rate constants and the base potassium ethoxide. Figures 12 and 13 show these plots.

The rate of condensation of p-nitrotoluene is almost twice that of the ortho isomer. This seems to be due to two factors. The slower reaction of the ortho isomer may be attributed in part to the greater steric hindrance to the reaction of the methyl group, and in part to greater difficulty experienced by the nitro group in attaining co-planarity with the aromatic ring. This co-planarity between the nitro group and the ring is essential in order that the resonance effects are fully operative. If activation of the methyl group is largely due to the resonance effects, then the para- compound would be expected to condense

TABLE XIV

Relative Rates of Condensation of o-, p-, and m- Nitrotoluene
with Ethyl Oxalate**

[Nitrotoluene] = [Diethyl oxalate] = [Sodium ethoxide] = 0.28 M.

Solvent, anhydrous ethanol. Reaction temperature, 76.3°

Nitrotoluene isomer	Fourth-order rate constant, $k_4 \times 10^{***}$ (liter ³ moles ⁻³ min ⁻¹)
<u>ortho</u> -	0.560
<u>para</u> -	1.04
<u>meta</u> -	no evidence of condensation*

* In a solution 0.5 M in reactants and using benzene and ether solvents, there appeared slight red colouration indicating a possibility of condensation; but under our conditions, no condensation occurred.

** The rate data are presented in Table XXX.

*** See footnote of Table XIII for the rate constant calculations.

TABLE XV

Substituent Effect on the Rate of Condensation of 4-Substituted
o-Nitrotoluenes with Diethyl Oxalate in the Presence of Sodium
Ethoxide²

[4-X-2-nitrotoluene] = [Diethyl oxalate] = [Sodium ethoxide] =
0.285 M. Ionic strength, 0.285. Solvent, anhydrous ethanol.
Reaction temperature, 76.3°.

4-X	$k_4 \times 10^*$ (liter ³ mole ⁻³ min ⁻¹)	k_4^X/k_4^H	σ_p^1
H	0.570	1.00	0.00
F	0.917	1.61	0.062
Cl	3.47	6.08	0.226
Br	4.90	8.59	0.232
I	5.77	10.1	0.276

¹ The sigma values taken from J. Hine. Physical Organic Chemistry, McGraw-Hill Book Company Inc., Toronto, Ont. 1956, page 72.

² The pertinent rate data are presented in Table XXXI.

* See footnote of Table XIII for the rate constant calculations.

TABLE XVI

Substituent Effect on the Rates of Condensation of Substituted
2-Nitrotoluenes with Diethyl Oxalate in the Presence of Potas-
sium Ethoxide³

[X-2-NO₂C₆H₃CH₃] = 0.0224 M. [Diethyl oxalate] = 0.358 M.

[Potassium ethoxide] = 0.403 M. Ionic strength, 0.403.

Solvent, anhydrous ethanol. Reaction temperature, 76.3.

Substituent X	Pseudo-first-order rate constant, $k \cdot 10^3$ * (min ⁻¹)	k_X/k_H	σ_p^1
4-H	4.72	1.00	0.00
4-CH ₃	2.09	0.445	-0.17
4-F	7.60	1.61	0.062
4-Cl	33.2	7.03	0.226
4-Br	38.2	8.09	0.232
4-I	44.0	9.32	0.276
3-Br ²	7.23	1.53	--

¹ Ref. footnote of Table XV

² The relative rate of the 3-Br-2-NO₂-toluene for the sake of comparison only.

³ The rate data are presented in Table XIXII.

* See footnote of Table V for the rate constant calculations.

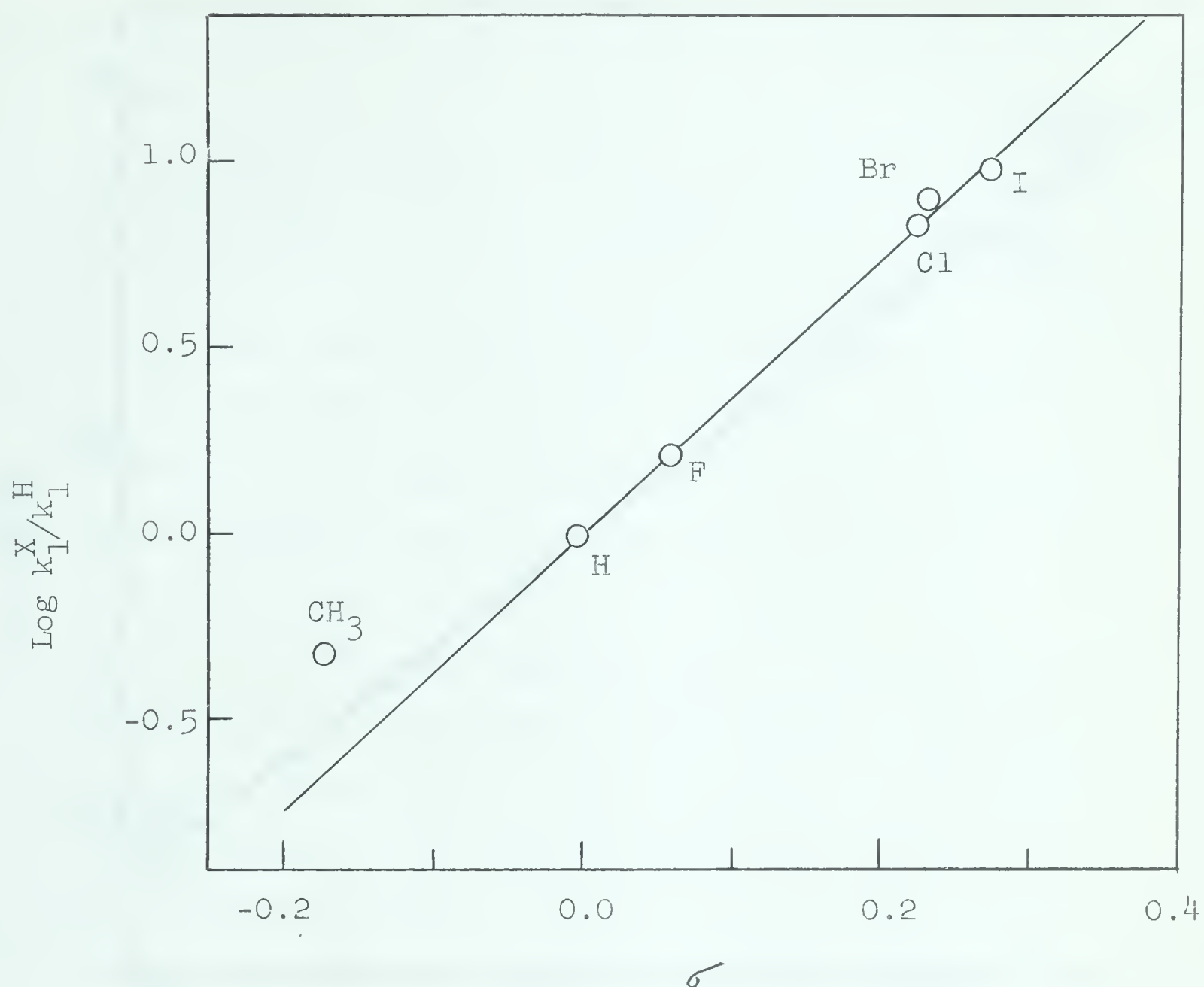


Fig. 12. Hammett σ plot for reaction of para-substituted o-nitrotoluenes with diethyl oxalate using potassium ethoxide as catalyst. Psuedo-first-order rate constants with respect to nitrotoluenes were employed.

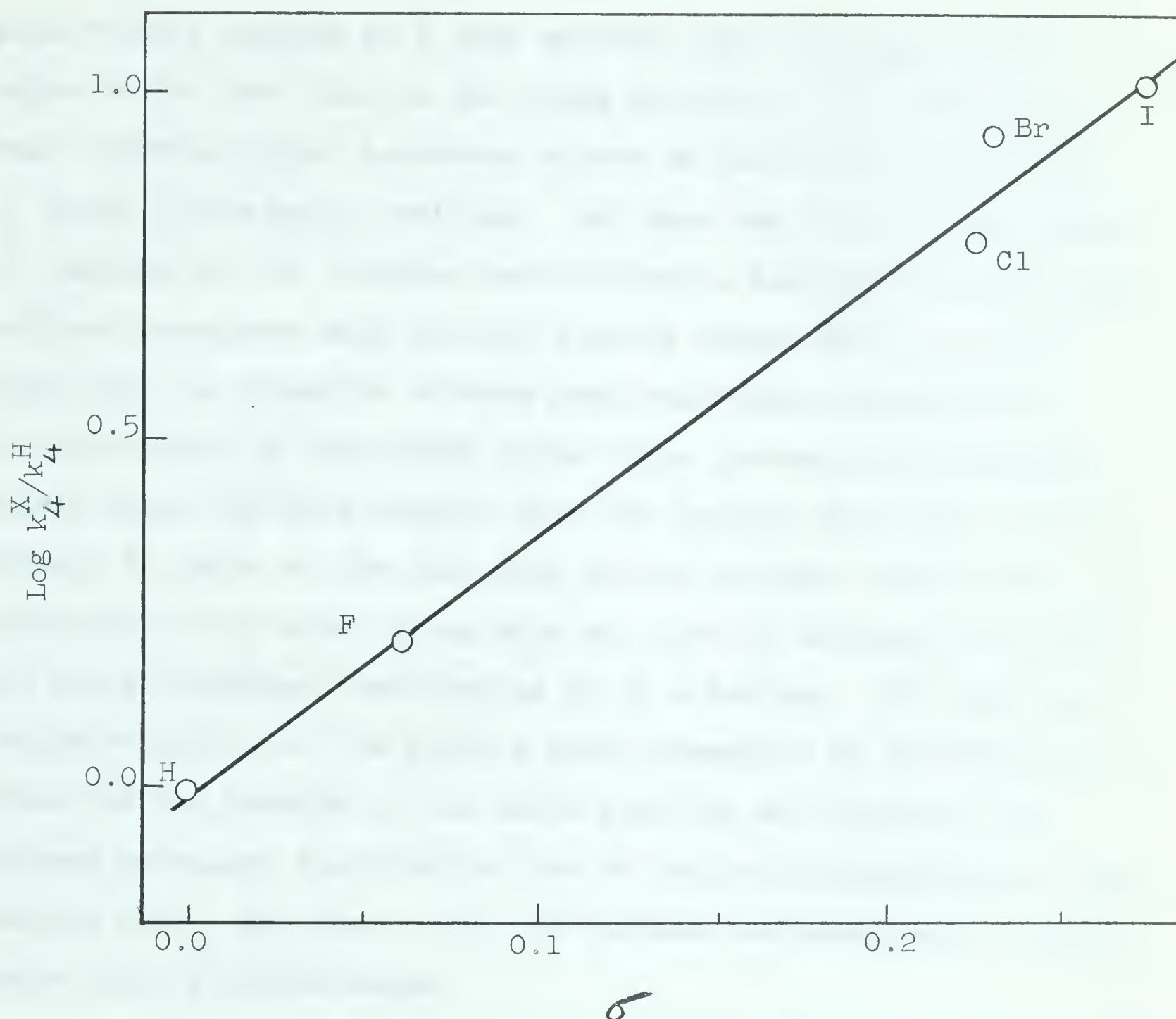
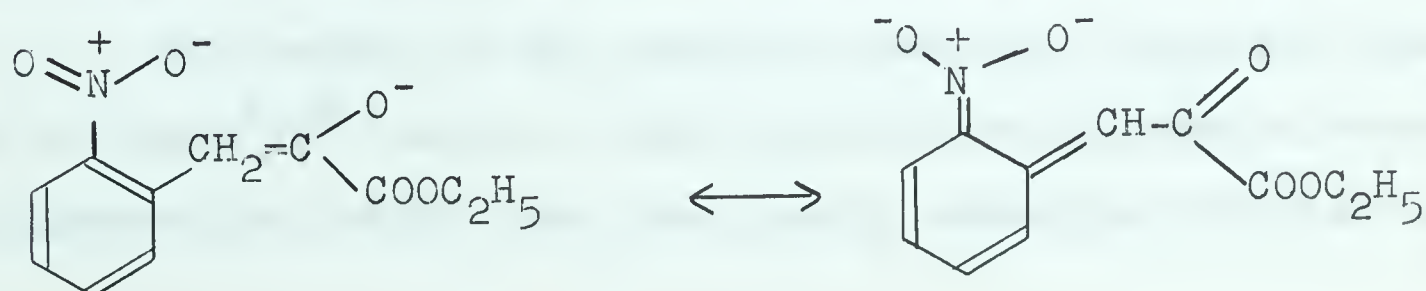


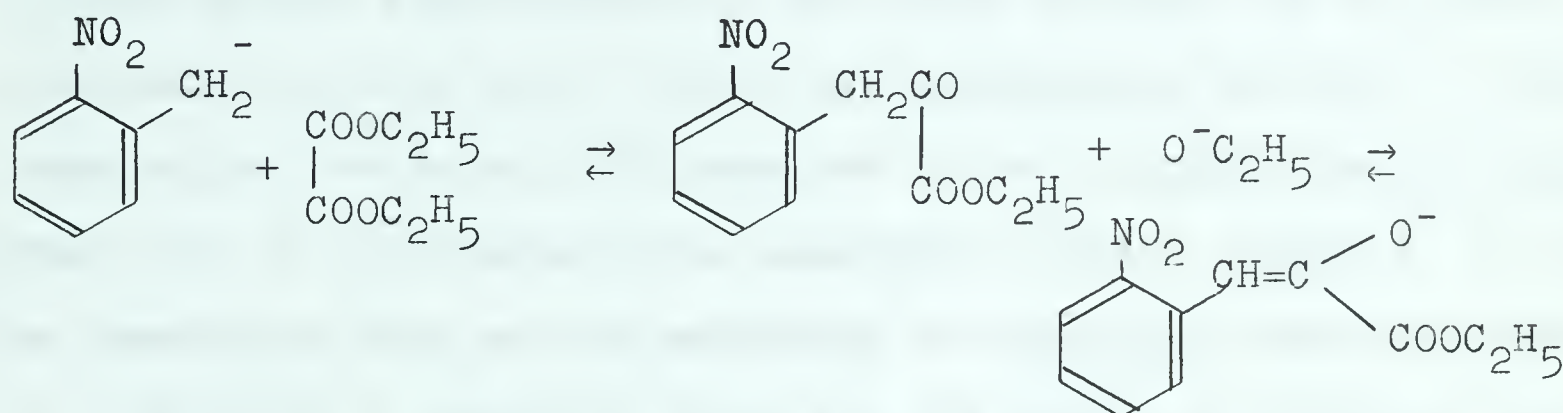
Fig. 13. Hammett ρ plot for the reaction of para-substituted o-nitrotoluenes with diethyl oxalate using sodium ethoxide as catalyst. Over-all fourth-order rate constants were employed.

with diethyl oxalate at a rate greater than the ortho isomer in spite of the fact that in the ortho position, the nitro group would exert a higher inductive effect on the methyl group than it would in the para- position. But when one compares the rates of reaction of the 3-bromo-2-nitrotoluene, 4-bromo-2-nitrotoluene, and 2-nitrotoluene with diethyl oxalate (Table XVI), it can be seen that the inductive effects must contribute considerably to the activation of the methyl group since 3-bromo-2-nitrotoluene reacts about 50% more rapidly with the oxalate than does 2-nitrotoluene in spite of the fact that in the 3-bromo- derivative, co-planarity of the nitro group with the ring is seriously affected, and hence resonance contribution is at a minimum. The increased inductive effect of the o-nitro group augmented by the inductive effect of the bromine in the three position may overcome the reduced resonance contribution due to the non-co-planarity of the 2-nitro group, and thus cause the 3-bromo-2-nitrotoluene to react faster than 2-nitrotoluene.

In addition a third factor affecting the reaction rate might be as follows. The product of the condensation, the α -keto ester, immediately enolizes in the basic reaction mixture. This enolate ion may be stabilized by the presence of the conjugated double bond system as shown below.



Thus the formation of the enol will be favoured by the nitro group in the ortho or (even more so) in the para position in the aromatic ring. The greater the stability of the enol, the more the equilibrium of the step in which the ketone is formed, is shifted to the right:



This stabilization of the enolate is much less when the nitro group is in the meta position and hence in the case of the condensation of the meta-nitrotoluene, the equilibrium of the reaction corresponding to the first step in the above equation will lie predominantly on the left. Therefore the m-nitrophenylpyruvate is not formed in any measurable amount.

Comparison of the rates of condensation of 3-bromo-2-nitrotoluene and 4-bromo-2-nitrotoluene with diethyl oxalate show a marked increase in the rate of condensation of the latter, a result not unexpected, since the nitro group can now be more coplanar, and thus exert a greater resonance effect, which in turn increases the stability of the carbanion as well as the enolate.

The values of the reaction constant ρ obtained from a plot of $\log k^X/k^H$ versus σ show an excellent agreement between the pseudo-first-order rate data, using potassium ethoxide as

base, and the over-all fourth-order rate data, using sodium ethoxide. The value of ρ obtained is quite high, +3.7, indicating the carbanionic nature of the transition state. This value is comparable to the 3.2 obtained by Streitweiser and Van Sickle (36) for the deuterium exchange reactions of deuterated toluenes containing methyl substituents in the ring, carried out in cyclohexylamine solvent with lithium cyclohexylamide catalyst. Although comparable, the value of ρ obtained by us is significantly higher than that of Streitweiser and coworkers (ibid). However, it must be remembered that we are measuring the over-all reaction constant, ρ , which is a composite value for the series of reaction steps (a) formation of the carbanion, (b) the reaction of the carbanion with the solvent to exchange a proton, and (c) the reaction of the carbanion with the substrate to cause the condensation. On the other hand, Streitweiser and Van Sickle have measured for the reaction of the formation of the carbanion alone. This may be the reason why our value is different from theirs.

D. Solvent Effects

The values of the equilibrium constant, reported in Table XII, are not entirely satisfactory, but they generally agree within a factor of 2. In order to establish an equilibrium between the reactants and products, the forward reaction of the formation of the product must be accompanied by the solvolysis of the pyruvate in a reverse reaction. This fact is confirmed by the evidence presented in the experimental section. (See Figure 14).

TABLE XVII

Solvent Effect on the Rate of Condensation of *o*-Nitrotoluene
with Diethyl Oxalate in the Presence of Sodium Ethoxide[†]

[*o*-Nitrotoluene] = 0.0947 M. [Diethyl oxalate] = 0.0943 M.
 [NaOC₂H₅] = 0.1039 M. Ionic strength, 0.1039.

Benzene/ethanol ratio (vol/vol)	Reaction temperature (°C) [*]	Initial rates of condensation X 10 ⁵ (moles/liter/min)	% Conversion to product at equilibrium
0:100	76.3	1.20	3.2
30:70	67.2	1.49	5.8
70:30	68.0	2.50	9.1
80:20	69.5	4.32	28.0 ^{**}
90:10	72.9	6.70	--- ^{***}
100:0	76.3	115.0	11.2

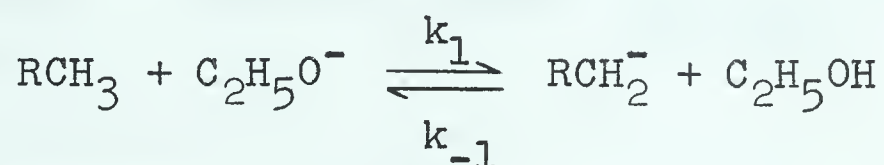
* Benzene-ethanol mixtures boil at lower temperatures than those of the two pure liquids.

** The product began to precipitate when the per cent conversion reached 28%.

*** Product precipitation began at the relatively low per cent conversion indicated.

† The pertinent rate data are presented in Table XXXIII.

To investigate the role of ethanol in the reaction, the solvent effect was studied by substituting ethanol by other solvents. Ethanol would be expected to take part in the reaction in two steps. Firstly, in the formation of carbanion from the nitrotoluene, the equilibrium of the reaction



(where R is $\text{O}_2\text{N C}_6\text{H}_4$)

will be influenced by the alcohol. Since o-nitrotoluene is a very weak acid, its anion will be expected to be a stronger base. Hence the exchange of proton from ethanol to the anion will be greater. Elimination of ethanol from the solvent will shift this equilibrium to the right and will enhance the rate of condensation. Secondly, ethanol takes part in solvolysis of the product, and elimination of ethanol from the solvent would push this equilibrium to the right.

Thus elimination of alcohol from the solvent would be expected to cause an increase in the rate of condensation and change in the equilibrium to higher conversion to the products. This was found to be the case when the reaction was carried out in solvents other than pure ethanol under comparable conditions. Since the reaction in alcohol was slight at lower temperatures, all of the rate studies were conducted at 76° . Diethyl ether was

TABLE XVIII

Temperature Coefficient of the Pseudo-First-Order Rate Constant
with Respect to *o*-Nitrotoluene *

Temperature (°C)	[<i>o</i> -Nitrotoluene]	[Diethyl oxalate]	[NaOC ₂ H ₆]	$k_1 \times 10^4$ *** (min ⁻¹)
76.3	0.0588	0.376	0.3904	23.5
53.6	0.0604	0.386	0.4023	3.87
35.1	0.0619	0.396	0.4122	0.576

* The pertinent rate data is presented in Table XXXIV.

*** See footnote of Table V for the rate constant calculations.

unsuitable at this high temperature.

Diethyl oxalate was found to be a good solvent, giving a rate of condensation higher than that found in any other solvent. However, product precipitation took place almost immediately. The higher rate of reaction is not unexpected and is due to the elimination of ethanol as solvent, and to the effect of the law of mass action (since diethyl oxalate is one of the reactants).

Benzene was found to be a satisfactory solvent for the Reissert condensation reaction. A study of the rates of condensation with different benzene-ethanol solvent ratios was conducted at 76.3°. The results of this study are summarized in Table XVII.

It is seen from Table XVII that the extent of conversion to product does actually increase as the relative amount of ethanol in the solvent decreases. In benzene solvent, the rate of reaction is very large, while the apparent conversion to products is very small. However, this effect is no doubt due to lower solubility of the product enolate in benzene. In the reaction carried out in 80% benzene, both the rate of condensation and the per cent conversion were higher. The greater rate of reaction and position of the equilibrium as one reduces the amount of alcohol in the solvent emphasizes the role of solvolysis of the product to the original reactants.

E. Activation Energy

The activation energy of the Reissert condensation reaction was determined by measuring the pseudo-first-order rate

constants of the reaction with respect to o-nitrotoluene at three different temperatures.

The activation energy ΔE is given by the Arrhenius equation

$$k = Ze^{-\Delta E/RT}$$

where k = rate constant of the reaction at temperature T° K, Z is the Arrhenius frequency factor, and R is the gas constant. Taking decadic logarithms, the above gives

$$\log k = \log Z - \frac{\Delta E}{2.303 RT}$$

Thus, plotting the logarithm of rate constant versus reciprocal absolute temperature, the value of ΔE was calculated. Table XVIII shows the results. The activation energy was found to be 18.5 kcal/mole. The Arrhenius plot of the temperature coefficient of the pseudo-first-order rate constants is shown in Figure 17, using the rate constants from Table XVIII.

F. Summary of the Results and Discussion

The data accumulated in the work described in the preceding pages shows that the Reissert condensation reaction exhibits the following prominent features:

1. The over-all kinetics appears to be of the fourth order, consisting of first-order with respect to each of o-nitrotoluene and diethyl oxalate, and an apparent second-order with respect to the ethoxide.
2. The effect of the change of ionic strength on the reaction rate is positive. The slope of the plot of v versus ionic strength is found to be 2.02. (v = initial rate).
3. A large positive value for σ of +3.7 is obtained for the Hammett plot.
4. Solvent effect shows that the elimination of ethanol from the solvent results in a very great increase in the rate of the reaction. The position of equilibrium moves to the right as the proportion of the ethanol in the solvent decreases.
5. The reaction is found to be reversible.

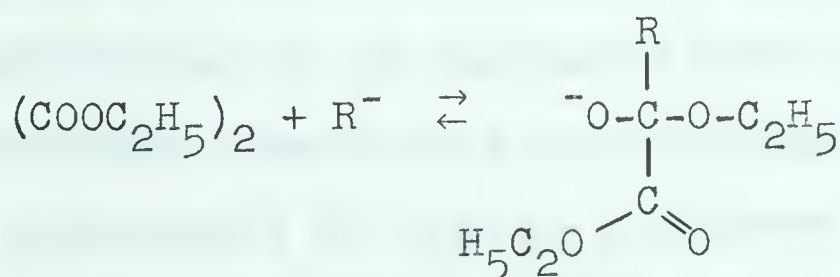
Mechanistic Interpretation of the Results

In order to find a mechanism which will account for all of the above observations, each of the various features will be considered in detail. The most surprising property of the reaction is that of second order dependence upon the base. This feature will be considered after the discussion of the others.

Salt Effects

The desirable conditions for the study of salt effects on the rates of reaction are (a) reactant concentrations of the order of 0.1 M or less, and (b) solvents of high dielectric constant. The concentrations used in this work is quite high (of the order of 0.3 M) and the solvent (ethanol) has a relatively low dielectric constant. For this reason, the Debye-Hückel equation could not be used. Similarly, the polar nature of the activated complex could not be deduced from the application of the plot of the equation $\log v/v_0 = 2AZ_ZZ_B \sqrt{\mu}$, since one of the reacting species, diethyl oxalate, is an electrically neutral molecule (37). Also, since potassium and sodium ethoxide are both strong bases and hence believed to be ionized completely (even though they may behave as ion pairs), the primary rather than the secondary salt effect is observed.

Because of the particular properties of the salts added, it is possible that the increased rate might be due to the addition compound arising from the combination of the acetate or the iodide ions with the relatively electron-deficient carbonyl carbon atom of diethyl oxalate:



Since these added ions are better "leaving" groups, the attack of carbanion on the carbon atom at which this addition took place would be facilitated. However, it can be reasoned that the attack of the acetate or iodide ion on the carbonyl carbon atom of the ester is unlikely since they both would be in competition with the much stronger base ethoxide. Furthermore, the infrared spectrum of diethyl oxalate in ethanol with potassium acetate showed no diminishing of the intensity of the carbonyl absorption peaks at 1765 and 1740 cm^{-1} . These facts argue against any addition compound, as shown above, being the cause of the accelerated reaction arising from added salt. It then seems that the effect of the salt additions is to increase the polarity of the solvent and hence increase the rate of ionic reaction.

Substituent Effect

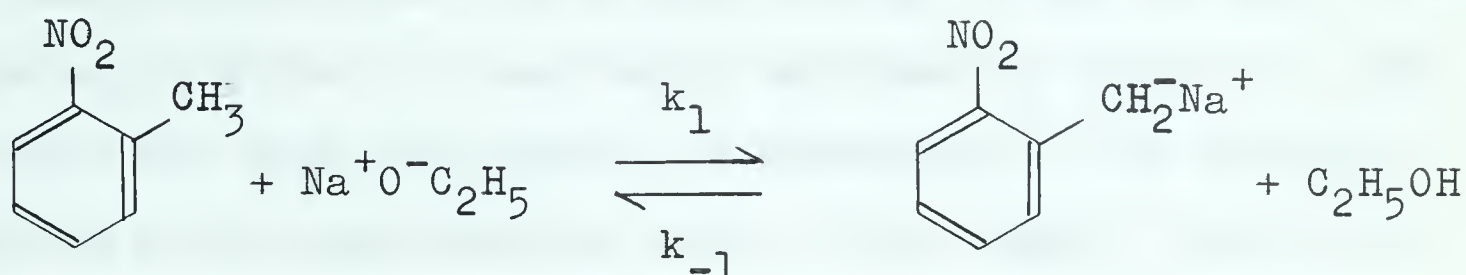
The plot of σ versus $\log k^X/k^H$ shows a high positive value of 3.7 for ρ . This clearly indicates that the formation of a carbanion is involved prior to or in the rate-determining step.

Solvent Effect and Reversibility

A change of solvent from ethanol to benzene and the increased concentration of the reactants both show increased rates and higher percentage conversion at equilibrium.

The replacement of ethanol by benzene as the solvent in the reaction would have a double effect on the rate. Firstly,

there is a marked effect on the formation of the carbanion according to the equilibrium:



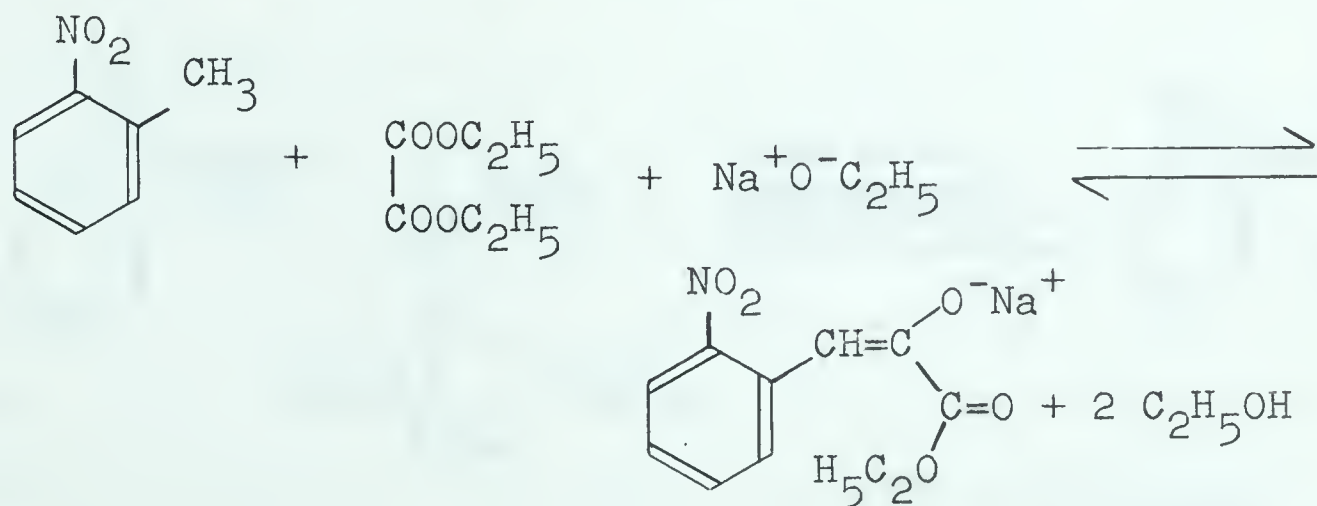
Since *o*-nitrotoluene is a very weak acid, its conjugate base would be expected to be very strong. Furthermore, in ethanol solution, the carbanion thus formed, being surrounded by an envelope of ethanol molecules, would tend to abstract a proton from the solvent, and revert to the original material. In this case, it would be expected that $k_{-1} > k_1$. On the other hand, if the ethanol is replaced by an aprotic solvent, the reverse reaction will be reduced and the carbanion would have more of a chance to react with the oxalate substrate, thus causing the condensation to occur at a higher rate. Secondly, since the dielectric constant of benzene is very low, the solvation of the ethoxide will be at a minimum, thus increasing its reactivity.

The reversibility of the reaction was clearly demonstrated by carrying out two experiments. In one, starting from a certain concentration of the reactants, *o*-nitrotoluene, diethyl oxalate and

sodium ethoxide, the reaction was allowed to attain equilibrium, and in the second, the product, ethyl o-nitrophenylpyruvate and sodium ethoxide in the same theoretical concentrations were allowed to attain equilibrium. It was found, as shown by Figure 14, that in both runs the same equilibrium concentration of the pyruvate was attained within experimental error. The slightly lower concentration in the reverse reaction may be attributed to the introduction of small amounts of moisture due to the prolonged reaction time. Any moisture will tend to destroy the base by hydrolyzing the oxalate (41). This reversibility of the Reissert condensation makes it strikingly similar to the Claisen condensation.

The observed kinetics suggests that there are four reacting species involved in the reaction sequence prior to, or in, the rate-determining step; namely, one molecule of o-nitrotoluene, one of diethyl oxalate and two of the ethoxide.

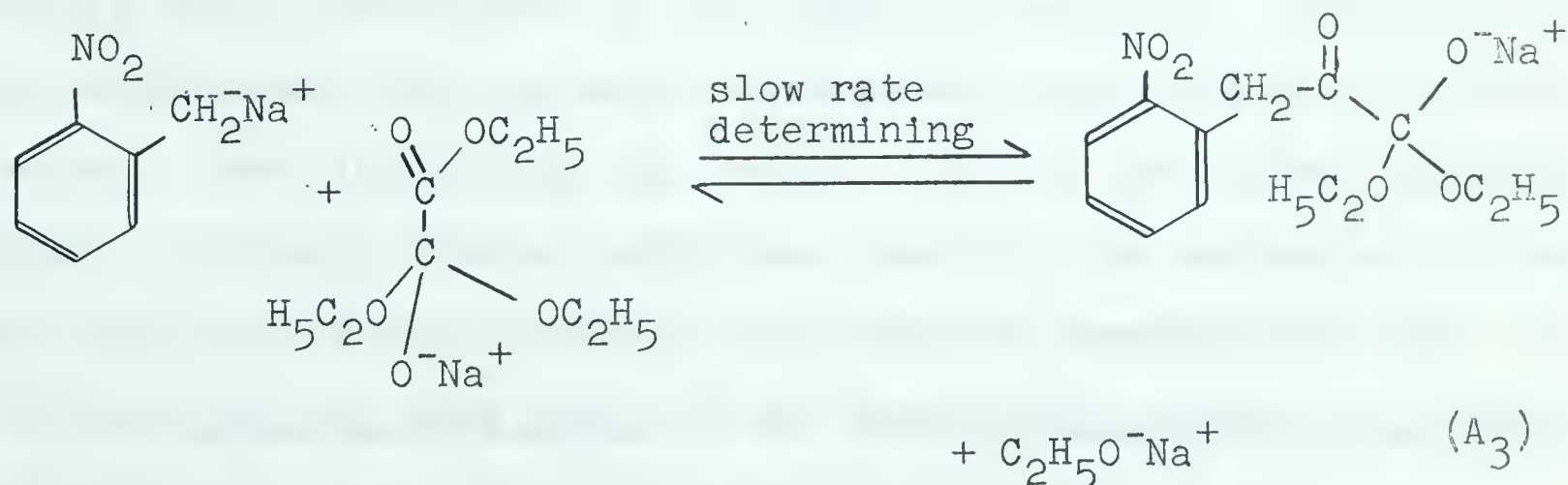
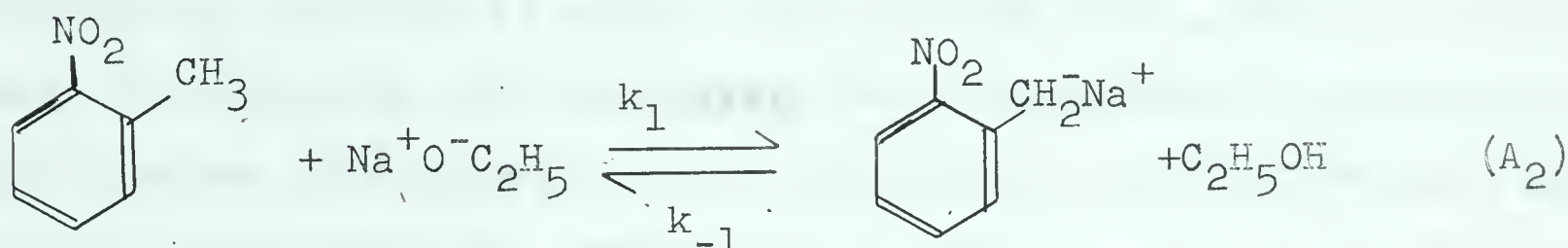
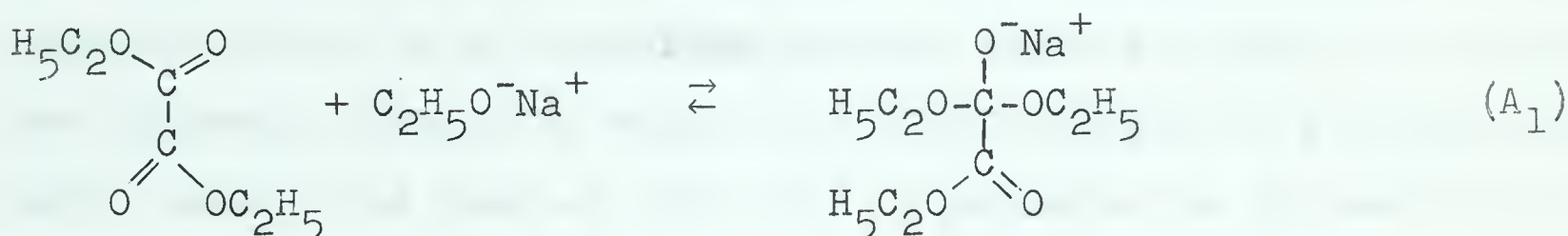
If one writes the stoichiometric equation for the reaction, it is seen that the reaction would be expected to show third-order kinetics at the most.

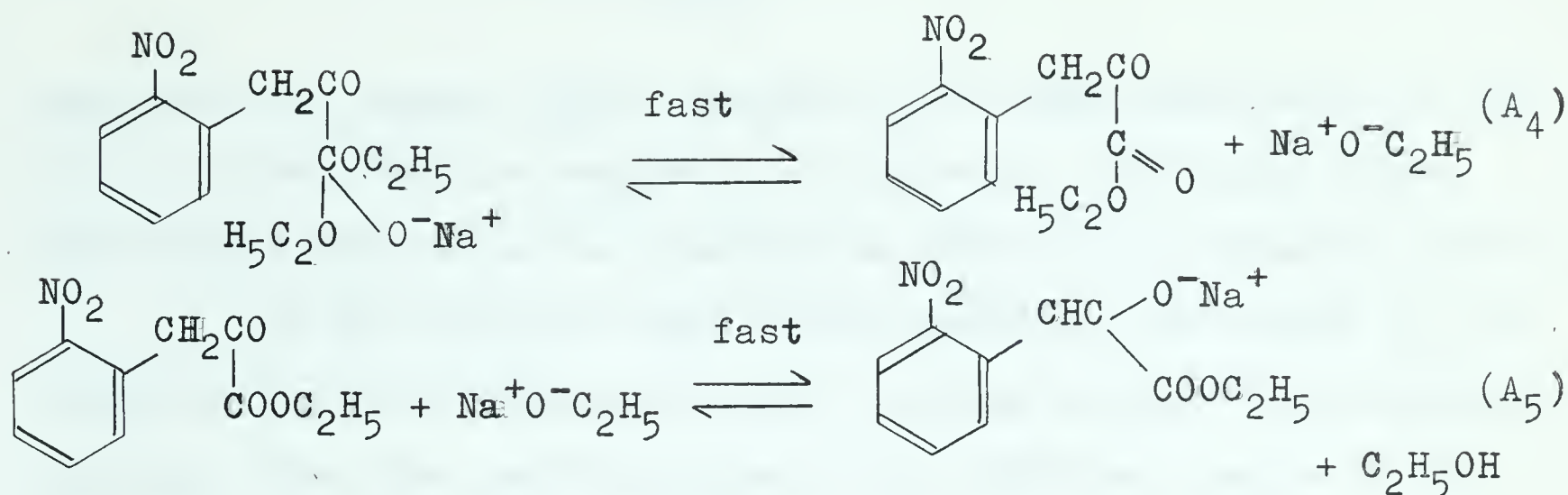


But the apparent second-order kinetics with respect to the base is a rather surprising and disturbing observation. There are two obvious possibilities for interpreting this result: either this is a correct observation and two ethoxide ions do actually take part in the reaction, or this is an erroneous result obtained due to some factor unaccounted for in the mathematical treatment of the kinetics of the base.

Proceeding with the first probability which assumes that the second order dependence upon ethoxide is correct, let us consider the validity of the following possible mechanisms.

Mechanism A



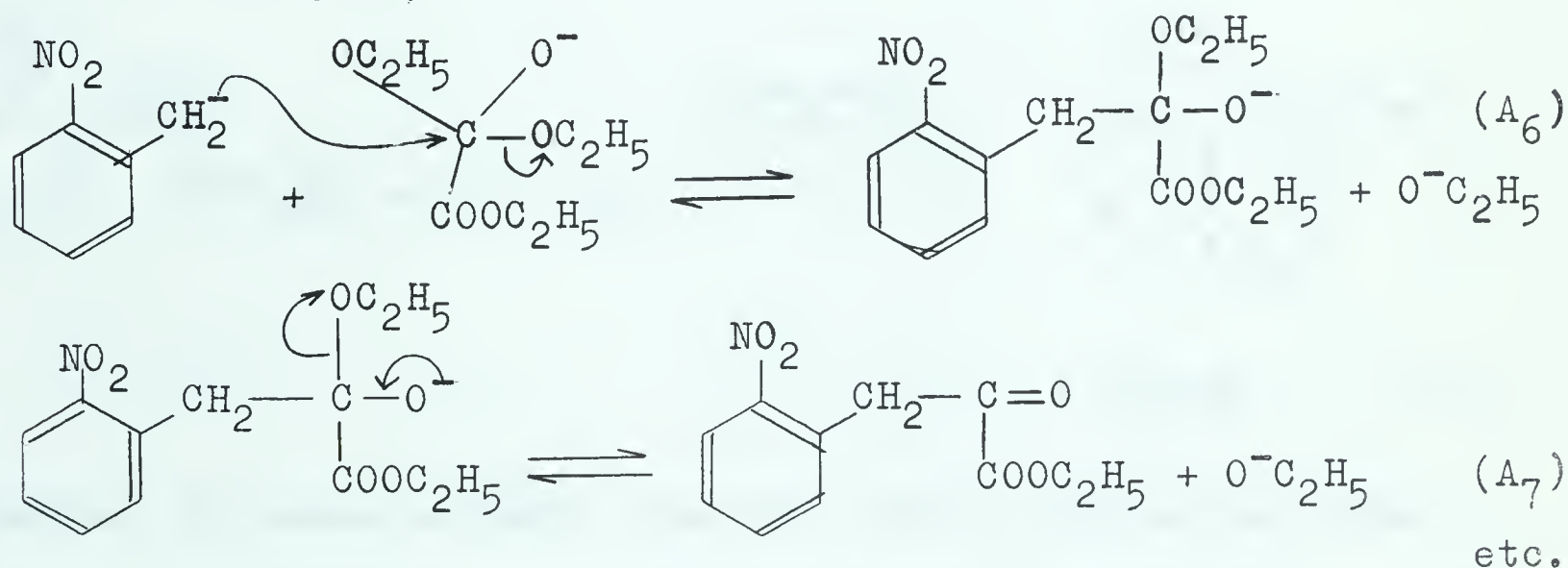


Adickes (41) isolated an addition compound when he mixed diethyl oxalate and potassium ethoxide in absolute ether solutions. He reported that the crystalline product was extremely hygroscopic and very readily hydrolyzed by traces of moisture. Bender (50) observed that, in di-n-butyl ether solutions, similar addition of sodium ethoxide took place readily. In the present work it was observed that, in an anhydrous diethyl ether solution, one of the two carbonyl absorption bands of diethyl oxalate at 1765 and 1740 cm^{-1} , namely the band at 1740 cm^{-1} , diminished in intensity as an increasing quantity of sodium ethoxide was added, and was minimum when the ethoxide and the oxalate were in equimolar proportions. Any further additions of sodium ethoxide did not affect the remaining band at 1765 cm^{-1} . This indicated that one of the carbonyl groups could participate in the addition reaction. Adickes (ibid) has shown that only one mole of ethoxide can be added to diethyl oxalate, thus indicating the incapability of the second carbonyl group to undergo similar addition. However, the unchanged intensity and position of both bands in the infrared demonstrated that such addition did not take place to any measureable extent in ethanol solvent even when the ethoxide to diethyl oxalate ratio was as

much as 4:1. Bender (ibid) arrived at the same conclusion in his study of the addition compounds of the ethyl trifluoroacetate with sodium methoxide. He observed no addition in methanol solvent.

If the reaction were to be caused by the attack of the carbanion on the electron-deficient carbon atom of the uncomplexed carbonyl, then the participation of the addition complex in the reaction would be conceivable as shown in mechanism A. However it is difficult to imagine an anion reacting predominantly with a relatively less electron-deficient carbonyl carbon atom of the adduct, present in very low concentration, when there is in the solution a higher concentration of the uncomplexed diethyl oxalate containing more electron-deficient carbonyl carbon atoms.

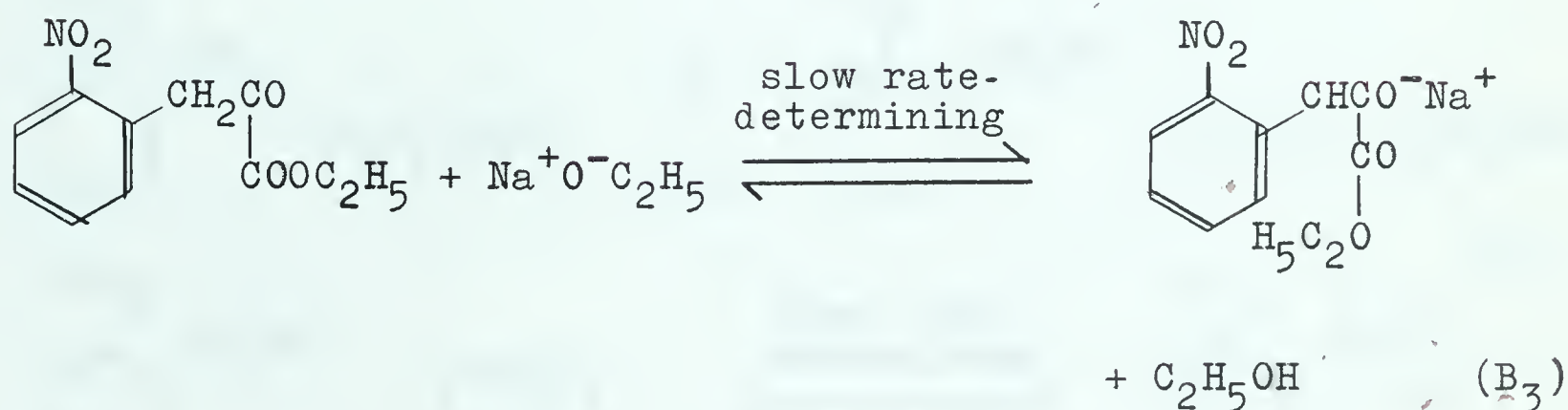
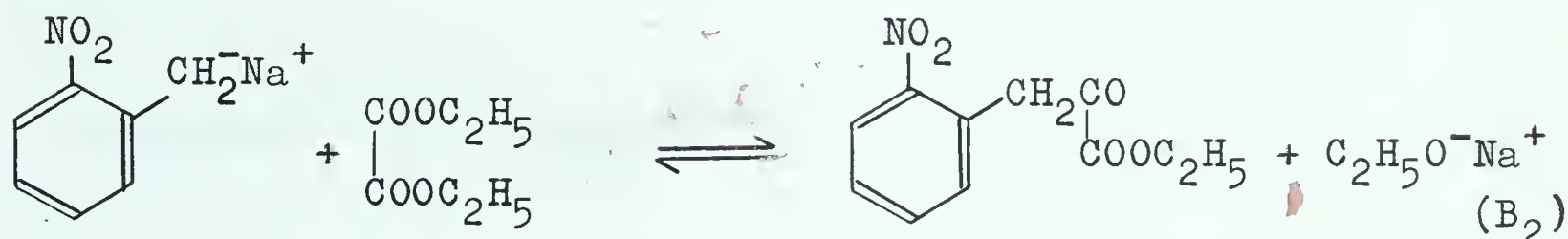
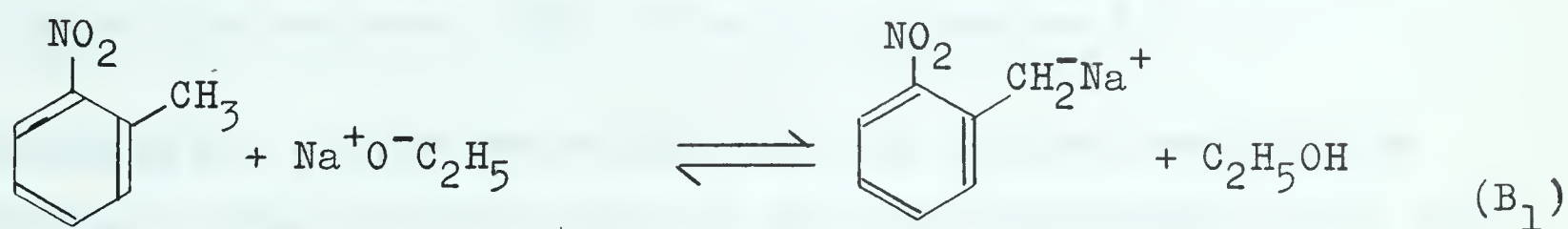
However, if the reaction is caused by an S_N2 type attack of the carbanion on the carbon atom that has undergone the addition in the following way:



then also, the addition complex could take part in the reaction, and the fourth-order kinetics would be explainable. In the absence of more experimental data and conclusive evidence, it is not possible to accept this as the mechanism, and yet at the same

time, it cannot be completely rejected.

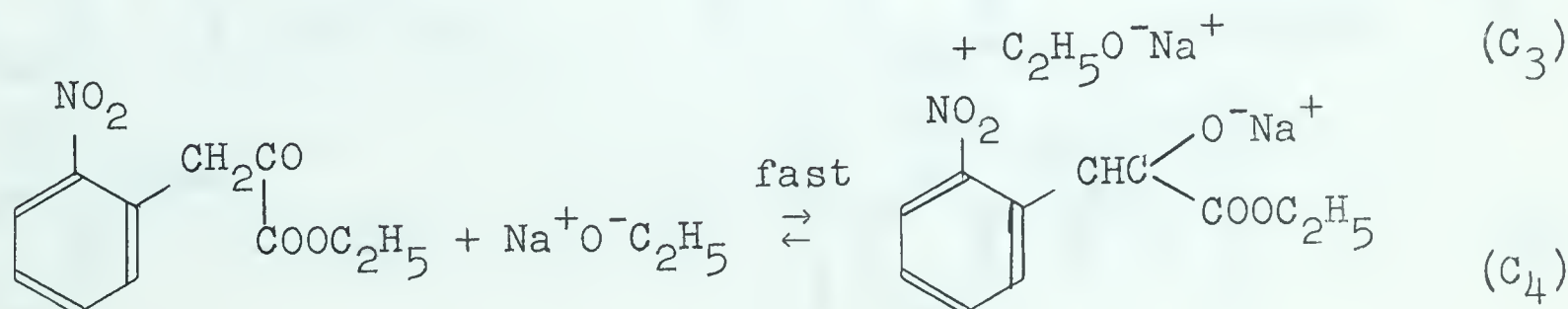
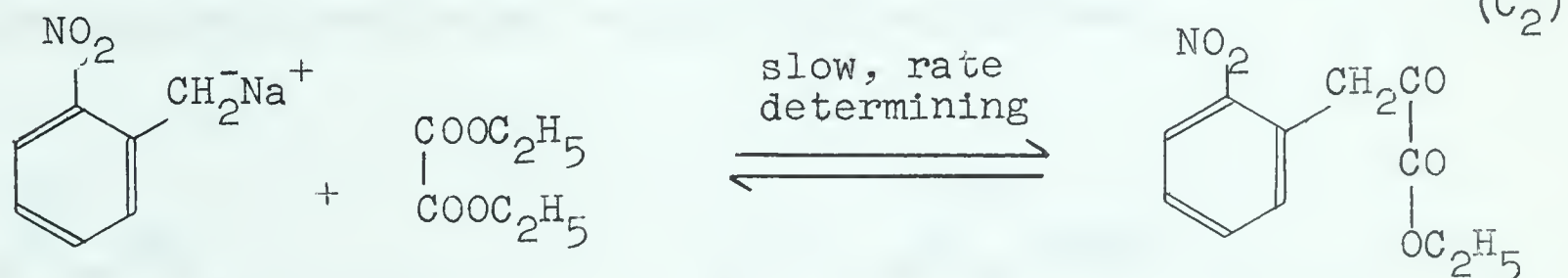
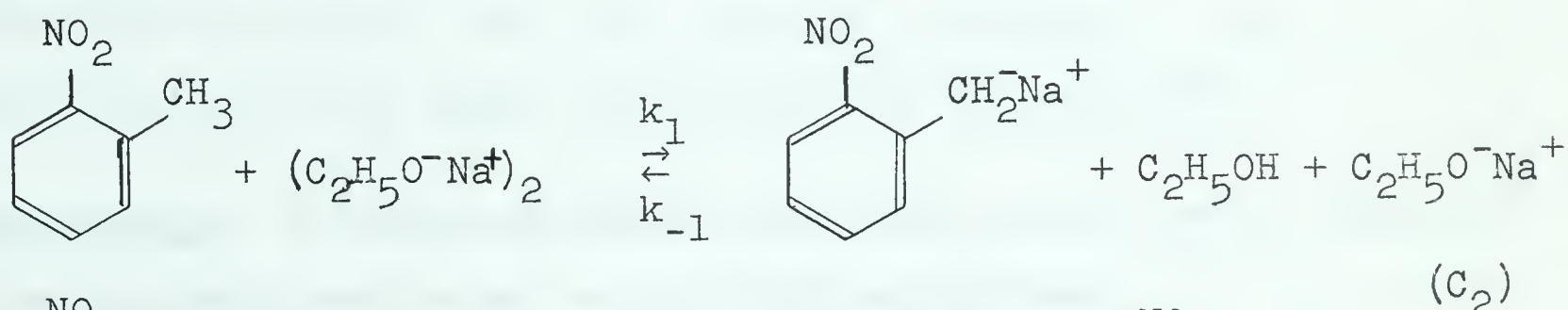
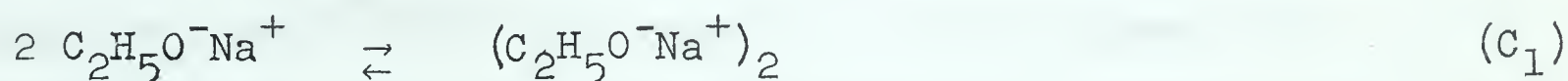
Mechanism B. If we consider the following sequence, the fourth-order kinetics would be imperative if step B₃ were the slow, rate-determining step.



However, it seems unlikely that the proton abstraction from a highly electron-deficient methylene group (flanked by a carbonyl group on one side and an electronegative aromatic ring on the other) should be a slow step, especially when compared to a

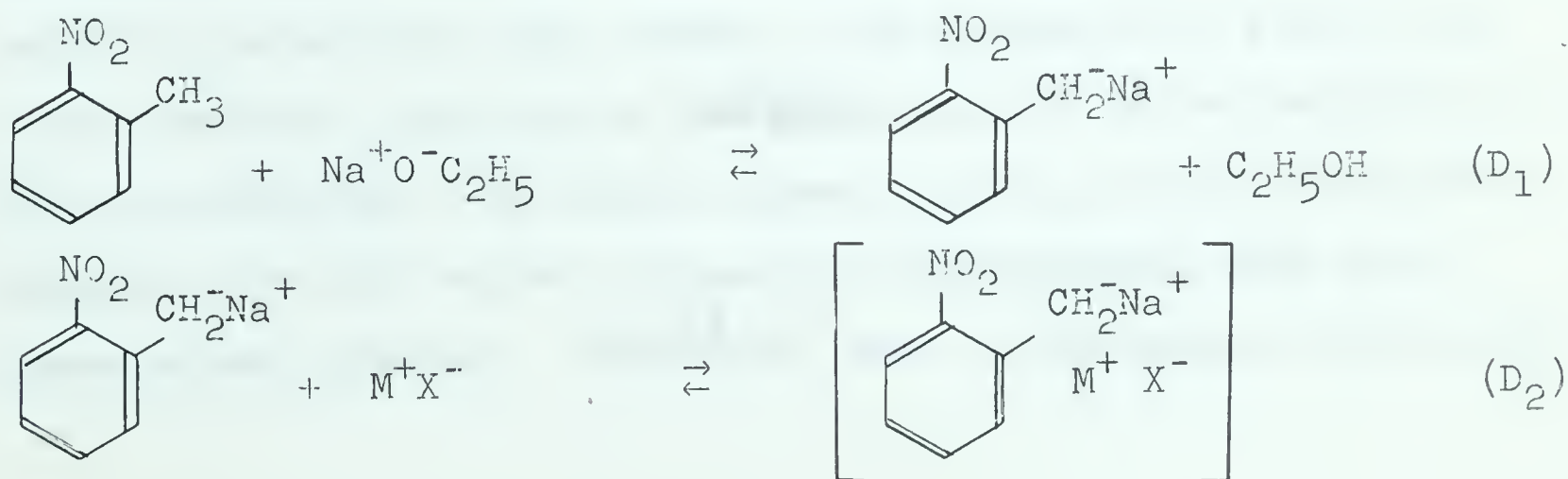
similar and more difficult process involved in an earlier step (B_1) in the reaction sequence - the formation of the carbanion. Furthermore, it has been observed qualitatively, that addition of ethanolic sodium ethoxide to an ethanol solution of ethyl *o*-nitrophenylpyruvate gave an instantaneous production of the deep red color of the enolate. This rules out mechanism B.

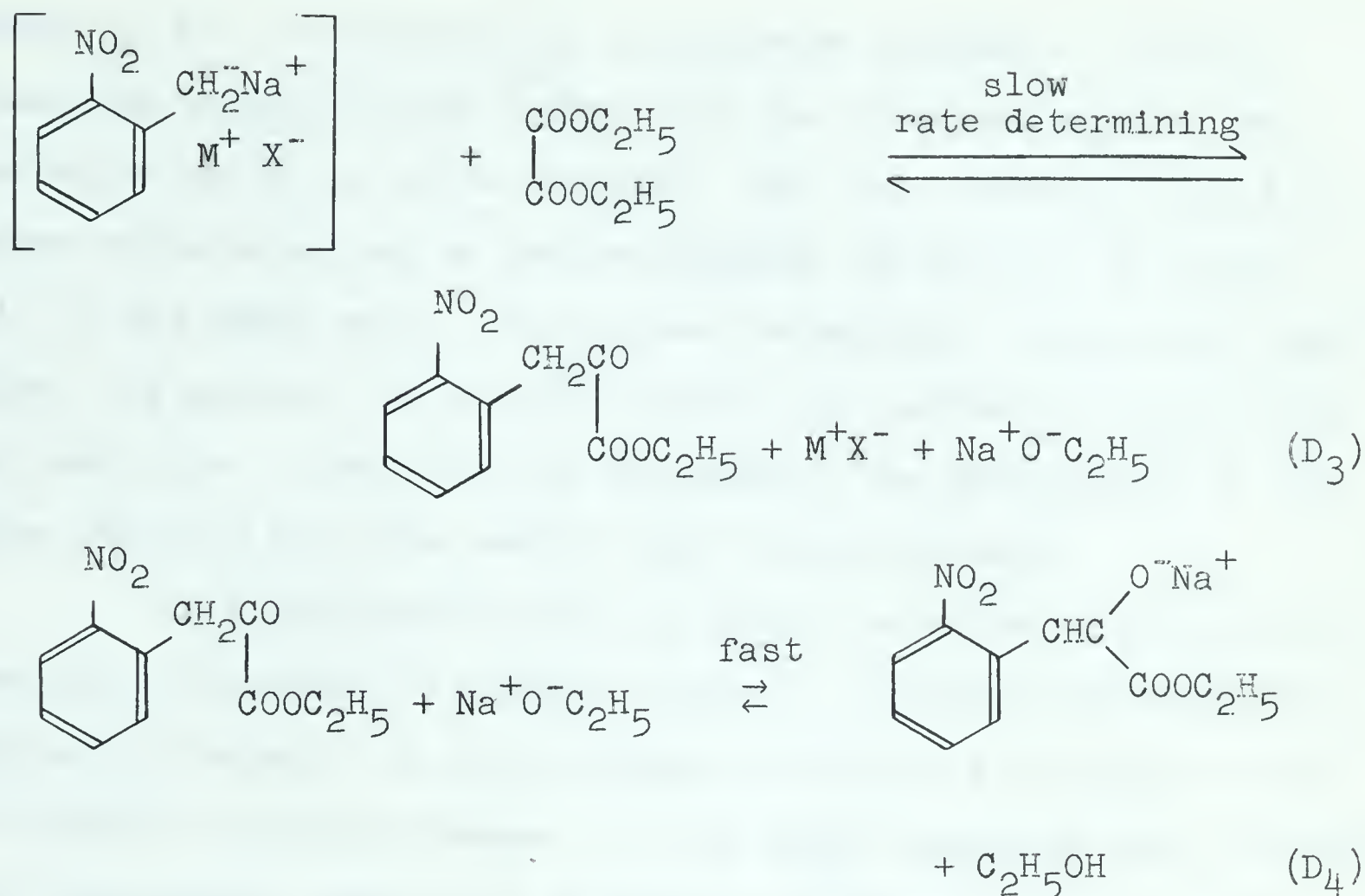
Mechanism C. A third mechanism that may include two ethoxide moieties in the reaction prior to the rate-determining step, would be as follows:



The essential feature of this mechanism, which would account for the second order dependence upon the formal concentration of base, is the formation of the ion quadruplet $(C_2H_5O^-Na^+)_2$. It is necessary that the equilibrium be established quickly and lie far to the left thus giving $(C_2H_5ONa)_2 = K(C_2H_5ONa)^2$. Evidence for the existence of ion quadruplets of this type has been given by Kraus (38) from the studies of dioxan-water mixtures of dielectric constant 23 or less. Whether such aggregates actually occur under the conditions of the present experiments is not known (to the writer's knowledge) but might be possible to a small extent since the dielectric constant of ethanol is 24. Furthermore, this mechanism requires that the reaction of the toluene (step C₂) is very much faster with the ion quadruplet than with the "ion pair" $C_2H_5O^-Na^+$. The extent of solvation by ethanol of $C_2H_5O^-Na^+$ might be considerably greater than the extent of solvation of the ion quadruplet and thus cause this difference in rates. (36).

Mechanism D. A fourth mechanism that may account for the over-all fourth-order kinetics may be outlined as follows:





Ion quadruplets similar to that shown in step D₂ have been postulated by Ingold and coworkers (51) in the study of the solvolysis of alkyl halides in benzene solvent. If this were the actual mechanism of the Reissert condensation, not only would it account for the participation of two ethoxide ion pairs in the reaction sequence before the rate-determining step, but it would also explain the positive salt effect. The necessity of such an ion clump could be justified in the stabilization of the carbanion in the following way. As stated before, $k_{-1} > k_1$, hence, the proton transfer from the solvent ethanol to the carbanion must be an overwhelming reaction. Therefore, most of the anions formed must

return to the nitrotoluene by such proton exchange. In this situation, a stabilizing factor like the formation of the ion quadruplet would be quite probable. The ion quadruplet could be formed by an anion and a sodium ethoxide ion pair or by an ion pair of the added salt. By the same reasoning, the more the salt added, the greater the possibility for the carbanion stabilizing ion quadruplet formation, and the greater the possibility of the anion reacting with the oxalate and not the solvent.

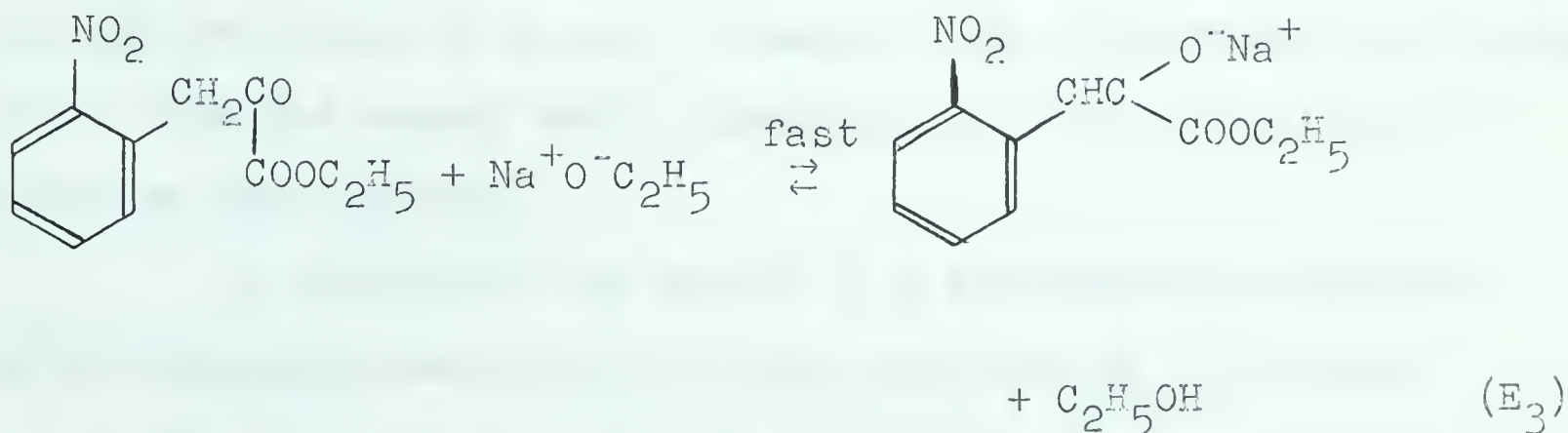
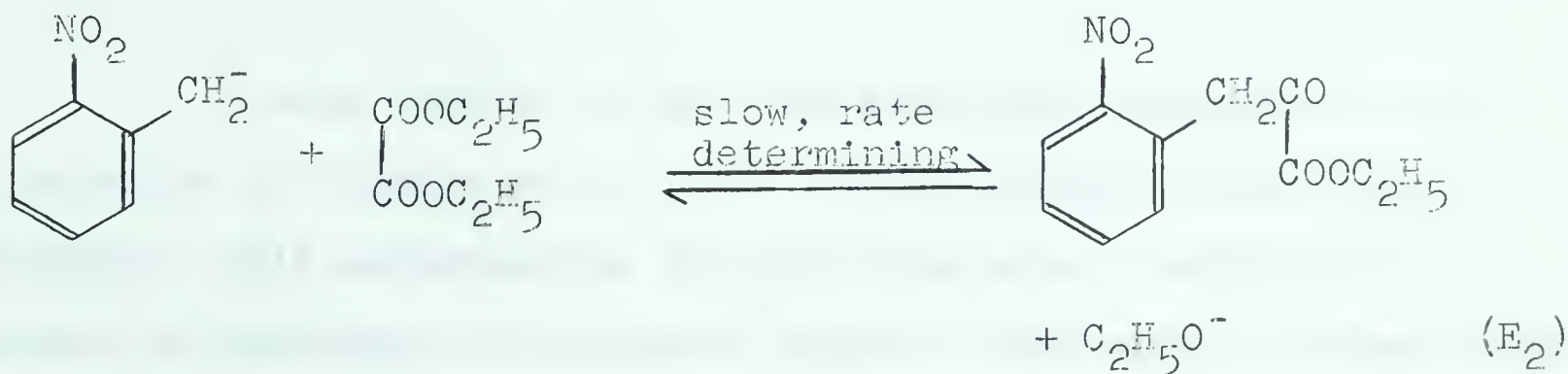
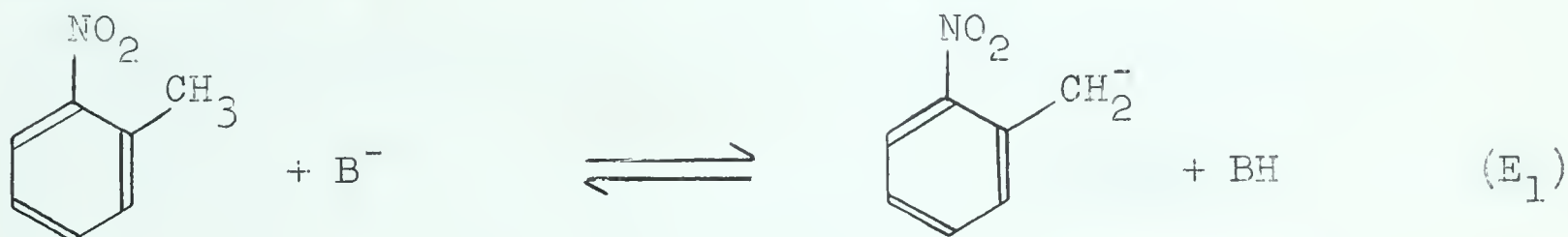
This postulate lacks any direct evidence of such an ion quadruplet formation in ethanol solvent. Although the dielectric constant of ethanol is of the order of 24, it is a solvent which can readily exchange protons. If the above reasoning were correct, then the kinetic order with respect to the base should steadily drop as the salt concentrations increase. This would be an interesting future study.

Another objection to the above postulate is that ions may be more prone to form aggregates with similar rather than dissimilar ionic species.

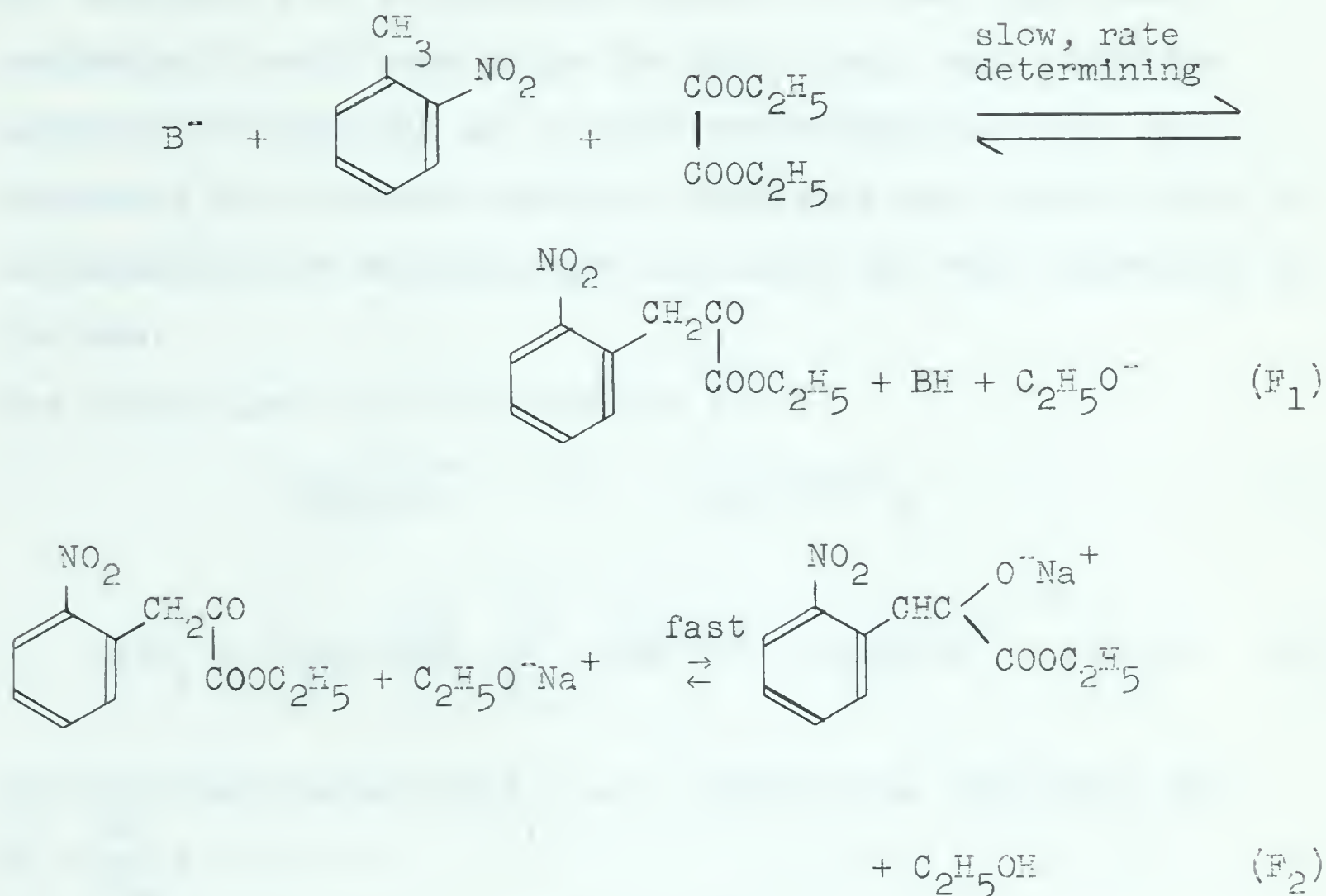
From the foregoing discussion, it seems that the second-order kinetics with respect to the base is rather difficult to explain in terms of actual mechanism. This could be a result of the mathematical treatment of the kinetic data, but here again, the question may be asked as to why the same kinetic treatment of the rate data with respect to o-nitrotoluene and diethyl oxalate should be satisfactory.

It is now necessary to consider the possibility that the second-order kinetics with regard to the base concentration may be fortuitous as far as the "actual" order is concerned. In this case the actual role of the base is to abstract a proton from o-nitrotoluene to produce the carbanion in a fast step, followed by the attack of the carbanion on a diethyl oxalate molecule in a rate-determining step. Thus, if one disregards the kinetic order of two and remembers that the role of the ethoxide is only to act as a proton-abstracting reagent, one can write two mechanisms for the reaction:

Mechanism E



Mechanism F

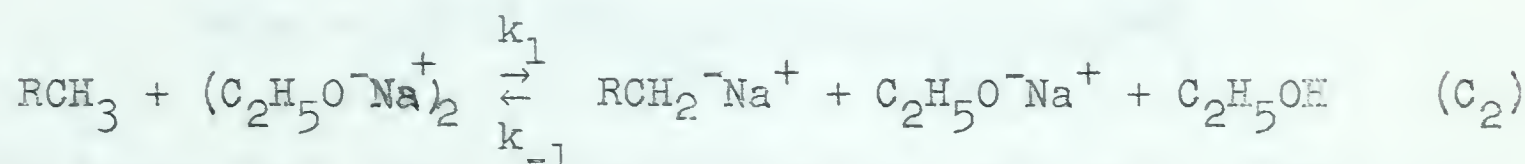
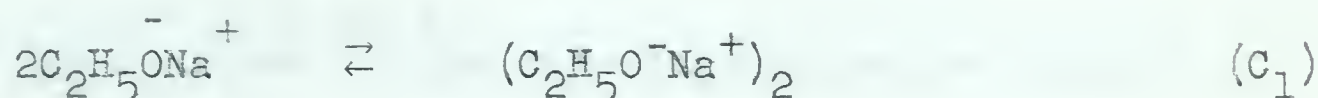


A case similar to the above has been reported in the literature by Tsurata et al (30). These workers found that in oxidative self-condensation of p-nitrotoluene in methanolic potassium hydroxide, the kinetic order of the base in terms of its activity was found to be two. However, the authors make no attempt to show how the second order dependence upon base fits into the mechanism they propose.

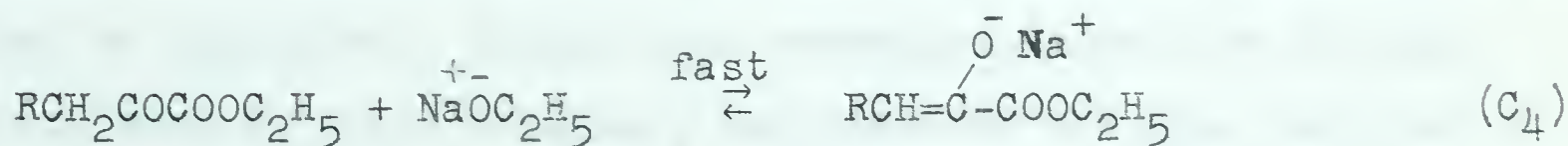
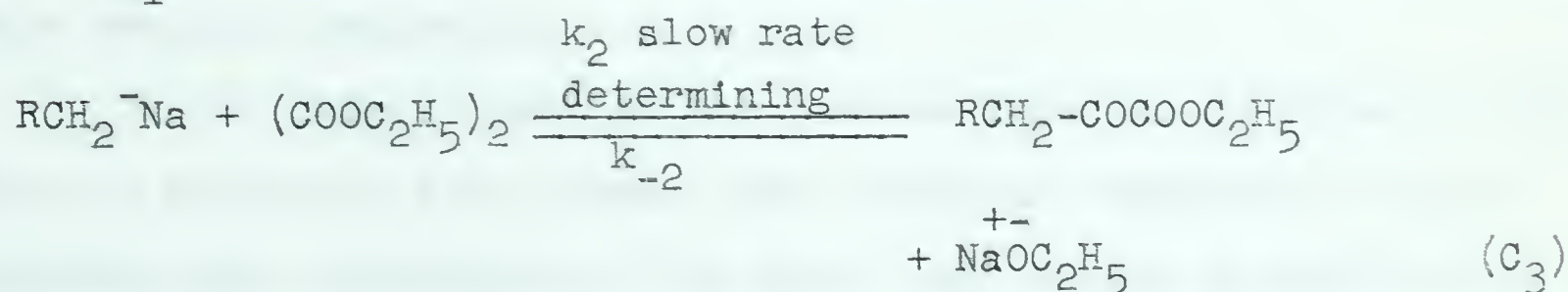
In conclusion the choice of a satisfactory mechanism for the Reissert condensation, rests entirely on (1) whether one accepts the second-order kinetics of the base as a fact or

(2) accepts it as a fortuitous result. In the first case mechanism C would seem to be the most likely one. From the sequence of reactions up to the rate-determining step, disregarding the reverse reaction since only the initial rates of condensation are measured, one can write the rate expression as follows:

The mechanisms C can be rewritten as:



(a fast equilibrium but $k_{-1} > k_1$ where R is $-\text{C}_6\text{H}_4(\text{NO}_2)$ and $K' = \frac{k_1}{k_{-1}}$)



$$\text{Initial rate } R = k_2 [\text{RCH}_2^-\text{Na}^+] [(\text{COOC}_2\text{H}_5)_2]$$

The concentration $[\text{RCH}_2^-\text{Na}^+]$ can be found from equation C₂ and is expressed as

$$[\text{RCH}_2^-\text{Na}^+] = K' [\text{RCH}_3] [(\text{C}_2\text{H}_5\text{ONa})_2]. \quad \text{The term } [\text{C}_2\text{H}_5\text{O}^-\text{Na}^+]$$

is neglected since ethanol is the solvent and it is not likely that $C_2H_5O^-Na^+$ will influence the proton transfer from the ethanol to the carbanion; if anything it will have the opposite influence. The concentration of the ethoxide ion quadruplet can be obtained from the equilibrium C_1 as

$$\left[(C_2H_5O^-Na^+)_2 \right] = K \left[C_2H_5O^-Na^+ \right]^2$$

Substituting these values in the rate expression one obtains

$$\text{Rate} = k_2 K K' \left[RCH_3 \right] \left[(COOC_2H_5)_2 \right] \left[C_2H_5O^-Na^+ \right]^2$$

If the assumptions made in the derivation are valid, then this rate expression does point to a second-order dependence on the formal concentration of the base, and mechanism C may be suggested as a possible mechanism.

In the second case, if one assumes that the function of the base is principally to produce the carbanion regardless of the observed rate dependence of the base, then either mechanism E or F may be suggested. Of the two, mechanism E seems to be more likely than F, since a ternary collision of the type required by the latter would be less probable.

Condensation of Poly-nitrotoluenes

To our knowledge no report appears in the literature showing successful condensation of 2,4-dinitrotoluene with

diethyl oxalate. In the attempts to condense 2,4-dinitrotoluene with diethyl oxalate in ethanolic solutions using sodium ethoxide as catalyst, we could not isolate the corresponding pyruvate but the solution first turned blue and then black. A tarry residue thus obtained gave only part of the original nitrotoluene back on neutralizing the base, and part of it was presumably lost in the simultaneous oxidation reduction reactions mentioned by Kermack (10) in connection with a similar condensation of 4-cyano-2-nitrotoluene. However, the same reaction was attempted using milder base, lithium ethoxide, with entirely satisfactory results. A good yield of the corresponding pyruvate was obtained.

m-Nitrotoluene could not be condensed by using even the more rigorous conditions of potassium ethoxide-ether medium. This failure to react may be due to the reduced reactivity of the methyl group. The nitro group in the meta- position is apparently incapable of exerting sufficient electron-withdrawing effect to activate the methyl group. The successful condensation of the 3-bromo-2-nitrotoluene demonstrates that the activation of the methyl group may not necessarily be caused by the resonance effect alone but require a certain threshold of electron-withdrawal which could be caused only by inductive effects of the substituents in the ring. This suggestion could be checked by looking into the possibility of the condensation of 3,5-dinitrotoluene, 2,3-dinitrotoluene and 2,4-dinitro-m-xylene. Similarly, the use of the above-mentioned mild conditions may be useful in condensing another

poly-nitrotoluene, 2,4,6-trinitrotoluene. If then by selecting the proper preferential reduction procedures, one could reduce the 2-nitro group in these compounds, the subsequent cyclization may produce the hitherto unreported ring-substituted nitroindole-2-carboxylic acids and thus the corresponding nitroindoles on decarboxylation.

EXPERIMENTAL

A. Preparation and Purification of Materials

(a) Solvents

Ethanol. Anhydrous ethanol was obtained by removing the water from commercially available 98% ethanol, as described by Fieser (42). The dried ethanol was stored in the dark under dry nitrogen.

Benzene. Commercially available thiophene-free benzene (analytical reagent) was dried over sodium wire and stored under nitrogen in the dark. No further purification of this benzene was carried out.

(b) Sodium and Potassium Ethoxides

Sodium and potassium metals were freed from their oxides and hydroxides by melting them in refluxing, stirred xylene or toluene under a slow current of purified dry nitrogen. When the metals had melted and formed shiny globules, the mixtures were cooled. These bright solidified globules were then removed from the flask and dissolved in anhydrous ethanol. The above manipulations were carried out in an atmosphere of pure, dry nitrogen.

The ethoxide prepared as above was standardized against sulphuric acid, and stored under dry nitrogen in a refrigerator. The cold ethoxide solutions were allowed to warm to room temperature before use in the experimental work. No ethoxide solution was kept longer than 3-4 days; fresh

batches were made quite frequently.

(c) Salts

Anhydrous reagent grade potassium acetate, obtained from the Fisher Scientific Company, was crystallized twice from commercial anhydrous ethanol and dried in an oven at 100° for two days.

Reagent grade sodium iodide, obtained from the Fisher Scientific Company, was crystallized twice from commercial anhydrous ethanol, and dried at 60° for two days.

Solutions (1.5 M) of these salts were made in anhydrous ethanol and the required volumes were used in kinetic runs.

(d) Reactants

o-Nitrotoluene. Eastman Kodak white label material was distilled twice under vacuum. Fractions boiling at 70-71° were collected at 2-3 mm. (B.p., 220° at 760 mm). Purity of this o-nitrotoluene was checked by refractive index measurements using a Pulfrich refractometer. Refractive index found after the first distillation, 1.5444 at 23°; after the second distillation, 1.5445 at 23°. Reported refractive index, 1.5473 at 20°. (43).

Diethyl Oxalate. Eastman Kodak white label material, found to be free of oxalic acid, was distilled to remove impurities. The fraction distilling between 180-182° at atmospheric pressure was collected and was redistilled at 2-3 mm. A middle fraction boiling between 39-42° was collected in two success-

ive distillations. There was no significant change in the refractive index of the ester in the two distillations under vacuum. Refractive index found using an Abbe refractometer, after the second distillation was 1.4103 at 19°. Reported, 1.4104 at 20°(44).

p-Nitrotoluene Eastman Kodak white label material was purified by crystallization. M.p., 50-51°. Reported m.p. 51-3° (44).

4-Fluoro-2-nitrotoluene. This compound, obtained from the Columbia Organic Chemicals Company, Inc., Columbia, S. C., U. S. A., was distilled under reduced pressure, and the fraction boiling at 93-95° at 3.5 mm was collected. Reported boiling point, 102° at 20mm (45).

2-Nitro-p-xylene. p-Xylene was nitrated according to the procedure described by Snyder and Pilgrim (20). The product was distilled under reduced pressure to remove unreacted p-xylene and the fraction distilling between 60-65° at 2 mm pressure was collected. The crude 2-nitro-p-xylene obtained was distilled again, and the fraction distilling between 65-67° at 2 mm was retained.

4-Chloro-2-nitrotoluene. Yellow label material from Eastman Organic Chemicals, Ltd., Rochester, N. Y., was recrystallized repeatedly from ethanol. The purified product melted at 38°. Reported m.p., 38.2° (46).

4-Bromo-2-nitrotoluene. 2-Nitro-p-toluidine was diazotized and bromine was introduced in the aromatic ring by the procedure described in Organic Syntheses, (47). The product was crystallized

from ethanol. M.p., 45-46°. Lit., 45.5° (48).

4-Iodo-2-nitrotoluene. This was prepared similarly by diazotization of 2-nitro-p-toluidine. M.p. of product, 60-61°, lit., 61° (49).

3-Bromo-2-nitrotoluene. Leggetter and Brown's procedure was used to prepare this compound (28).

Preparation of the Ethyl *o*-Nitrophenylpyruvates

Condensation of the nitrotoluenes with diethyl oxalate was accomplished by the procedure of Wislicenus et al (5).

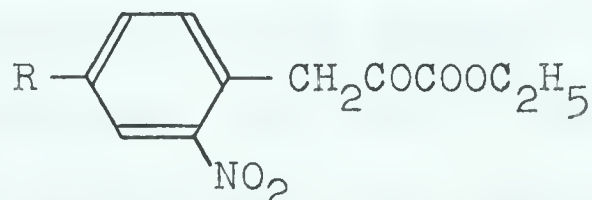
A portion of each of the esters so obtained was purified by chromatography on silica gel using pentane-benzene or pentane-ether mixtures as eluents. Neutral or basic alumina was unsatisfactory since a reaction occurred with the pyruvate such that it could no longer be removed by ether or acetone. Characteristics of the various esters prepared are shown in Table XIX.

B. Beer's Law Calibration Plots

All the ethyl nitrophenylpyruvates in the presence of base showed a very strong absorption at 458-460 $m\mu$ except in the case of 3-bromo-derivative which absorbed strongly at 400 $m\mu$. A calibration plot for each of these esters was obtained as follows. Sufficient quantities of the solid esters were accurately weighed in calibrated, 10 ml volumetric flasks so that when made up to volume with anhydrous ethanol, 0.01 molar solutions were obtained. With the aid of the λ pipettes, a series of volumes were withdrawn and added to 5 or 10 ml calibrated volumetric flasks

TABLE XIX

Physical Constants of Ethyl Esters of p-Substituted o-Nitrophenyl-
pyruvic Acids



R	Colour, etc.	M.p. found (uncorrected)	Reported m.p.
H	pale yellow needles	46-47°	46-47° (6)
F	colourless fine needles	54°	unknown
Cl	yellow needles	115-116°	-a
Br	yellow needles	121-122°	-a
I	yellow needles	110-112°	-a
CH ₃	yellow needles	106-108°	-a
Ethyl 3-bromo-2-nitrophenyl pyruvate	colourless platelets	115-117°	114-115° (28)
Ethyl p-nitrophenyl pyruvate	deep yellow crystals	106°	106° (6)

(a) Corresponding acids have been reported in the literature but no mention of the ethyl esters appears.

which were made up to volume by addition of 0.1 molar ethanolic sodium or potassium ethoxide. Care was taken that in each case the amount of 0.1 M ethoxide added was in a large excess of (100 times or more) the amount necessary to convert the pyruvate to its enolate. This large excess of base ensured practically complete conversion to the enolate. Well-mixed solutions from these glass-stoppered volumetric flasks were then immediately transferred to stoppered, rectangular, quartz absorption cells of 10 mm path length and the absorption measured at $458\text{ m}\mu$ in a Model B Beckman Spectrophotometer. The readings were taken against a blank, consisting of a matched cell containing only the 0.1 M ethanolic ethoxide solution. Details of a sample calibration are shown in Table XX.

C. Apparatus

The reaction was carried out in a 500 ml standard taper, 4-necked, round-bottom flask. The apparatus was equipped with an efficient water condenser and a stirring assembly. A 1000 λ pipette, attached at its upper end to a syringe, extended through a sleeve in such a way that the tip of the pipette was near the bottom of the flask. The upper end of the pipette and syringe was held to the sleeve by a piece of rubber tubing so that neither moisture nor air could enter the system nor vapors leave the system, but still allowed the removal of the pipette and syringe with a 1-ml aliquot of reaction mixture. The fourth opening of the

TABLE XX
Data for the
Calibration Plot for Ethyl 4-Fluoro-2-nitrophenylpyruvate

Volume of 0.01 M solution of ester added	Concentration of ester in 10 ml of solution, $\times 10^5$ (moles/liter)	Absorbance at 458 m μ		Average Absorbance
		Aliquot I	Aliquot II	
10	1.00	0.031	0.035	0.033
20	2.00	0.072	0.075	0.0735
50	5.00	0.184	0.182	0.183
100	10.00	0.371	0.372	0.371
200	20.00	0.772	0.770	0.771
300	30.00	1.145	1.145	1.145
400	40.00	1.542	1.540	1.541

The plot obtained from this data showed excellent agreement with Beer's Law.

flask permitted the addition of nitrogen which blanketed the mixture. A calcium chloride drying tube protected the condenser system from the moisture of the air. The reaction flask was immersed in a constant temperature bath at 76.3°C .

Prior to an experiment, the apparatus was flushed with dry nitrogen for 10 minutes. The sampling pipette and syringe was replaced by a jacketed dropping funnel which permitted pre-heating to 76.3° of the last constituent of the reaction mixture prior to its addition to the contents of the flask. This pre-heating required about 15 minutes. After rapid addition of this last reactant, the funnel was replaced by the syringe and pipette. Time measurements were begun upon complete addition of the last reactant.

Before removal of a sample of the mixture, the pipette was repeatedly flushed with the reaction mixture, and then the 1-ml aliquot was withdrawn and immediately added to 0.1 M ethanolic ethoxide in appropriate volumetric flasks of 10, 25, or 50 ml capacity. The dilution and resultant cooling was sufficient to quench the reaction. Following thorough mixing, the solution was then transferred to the rectangular cell and its absorbance measured in a Model B Beckman Spectrophotometer against a reference cell containing only the 0.1 N ethoxide.

To ensure complete conversion of the pyruvate to its enolate, care was taken that each aliquot removed from the reaction flask was diluted with 0.1 M ethoxide so that at least a 100-fold excess of base was added. Sufficient additional dilution was also

necessary in some cases in order that the absorbance could be measured accurately on the spectrometer.

The data for a typical run is illustrated in Table XXI .

D. Isolation and Identification of the Products of Solvolysis of Ethyl *o*-Nitrophenylpyruvate by Ethanolic Sodium Ethoxide

Ethyl *o*-nitrophenylpyruvate (7.1 g, 0.03 mole) was dissolved in 50 ml of anhydrous ethanol and 15 ml of 2 M sodium ethoxide (0.03 mole) solution in dry ethanol was added. The volume was made up to 100 ml and the mixture then kept in a thermostatted bath at 76.3° for 24 hours. After this time, the solution was carefully neutralized with gaseous HCl and then all of the alcohol was removed under reduced pressure. The remaining mass was extracted three times with dry ether and the combined ether extracts dried over magnesium sulphate. After almost complete removal of the ether, small samples of the residual solution were analyzed by vapor phase chromatography on a Burrell K₂ Kromo-Tog using a column of celite coated with Apiezon L. The column temperature was 187° C and the carrier gas, helium.

Ether, diethyl oxalate, and *o*-nitrotoluene were identified (with relative retention times in the order, ether > diethyl oxalate > *o*-nitrotoluene) by comparison with an authentic mixture of these three components.

Success in the isolation depends upon careful exclusion of moisture from the reaction and during the isolation procedure at least as far as the neutralization step, since sodium ethoxide

TABLE XXI
A Typical Kinetic Run
Experiment No. 73

$[\text{o-Nitrotoluene}] = 0.0588 \text{ M}^1$. $[\text{Diethyl oxalate}] = 0.376 \text{ M}$.
 $[\text{NaOC}_2\text{H}_5] = 0.390 \text{ M}$. Ionic strength, 0.39. Solvent, anhydrous
ethanol. Reaction Temperature, 76.3° .

Time (min.)	Absorbance X dilution factor	Concentration of ² enolate, X 10^3 (M)
0	0.0	0.0
2	0.090 X 10	0.248
5	0.239 X 10	0.66
8	0.391 X 10	1.08
12	0.599 X 10	1.66
16	0.810 X 10	2.24
20	0.989 X 10	2.73
25	1.20 X 10	3.10
30	0.569 X 25	3.95
36	0.670 X 25	4.65
46	0.839 X 25	5.30 ^a

¹ Concentrations of the reactants were calculated at 76.3° as shown in Appendix I.

² Concentrations of enolate obtained from appropriate Beer's Law calibration graph.

^a This corresponds to 12% conversion of the nitrotoluene to pyruvate.

in the presence of traces of water hydrolyzes ethyl oxalate rapidly to monosodium ethyl oxalate. For this reason, in all of our analyses, the proportion of oxalate to o-nitrotoluene was less than one, although the expected ratio is 1:1.

E. Search for Bimolecular Condensation Products from the Reaction Between Either p-Nitrotoluene or o-Nitrotoluene and Ethyl Oxalate in the Presence of Base.

To a mixture of 0.05 mole of each of p-nitrotoluene, diethyl oxalate and ethanolic sodium ethoxide was added enough dry ethanol to make 100 ml of solution (0.5 M with respect to each solute). The solution was then gently refluxed for 12 hours on a steam bath. To the deep red, viscous solution was added 100 ml of water and the resulting mixture was warmed on the steam bath for 20 minutes, whereupon the deep red colour faded somewhat. A further 100 ml of 50% ethanol in water was added and the whole was filtered. The small amount of precipitate thus obtained was washed free of unreacted p-nitrotoluene with 50% ethanol-water solution and then freed from residual p-nitrophenylpyruvate by washing with 10% aqueous sodium hydroxide until red filtrate ceased to appear. A water wash removed traces of sodium hydroxide. The residue was dried and weighed. The amorphous solid thus obtained was 1.8% of the theoretical yield of p,p'-dinitrobibenzyl expected from the p-nitrotoluene if all the toluene had reacted in this manner. The solid consisted essentially of the alcohol-

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insoluble substances, p,p'-dinitrobibenzyl and p,p'-dinitrostilbene and melted over a broad range, 190-290°.

A reaction carried out with potassium ethoxide yielded 2.5% of this mixture of crude products.

A similar pair of reactions performed with o-nitrotoluene gave no evidence of such side reaction products, thus supporting the statement that o-nitrotoluene is more difficult to condense into bimolecular products than is p-nitrotoluene (30).

Thus the amount of bimolecular product found in the case of p-nitrotoluene under our experimental conditions is not large enough to seriously affect the kinetics of the Reissert condensation and is apparently absent for o-nitrotoluene.

F. The Reversibility of the Reissert Condensation

The fact that ethyl o-nitrophenylpyruvate is decomposed into the original o-nitrotoluene and ethyl oxalate (1, 29) has led to the opinion that the Reissert condensation is reversible and resembles the Claisen condensation (29). Equivalent amounts of ethyl o-nitrophenylpyruvate and sodium ethoxide, left in dry ethanol for 8 days, gave a solution which contained o-nitrotoluene and ethyl oxalate, in agreement with Reissert's findings (1). These compounds were readily separable by vapor phase chromatography on a column of celite coated with Apiezon L. The amount of oxalate in this case was less than the expected equivalent of o-nitrotoluene. However, the method of its isolation caused much

unavoidable hydrolysis and thus explains this discrepancy.

In an attempt to show that the reaction is truly reversible, two experiments were performed. In one, the forward reaction, an anhydrous ethanolic solution of o-nitrotoluene, diethyl oxalate and sodium ethoxide in the concentrations 0.1750, 0.1750, and 0.1794 M respectively, was allowed to react at 76° until equilibrium had been reached as shown by the constant value for the optical density. This occurred after 1,110 minutes had elapsed. In the second experiment involving the reverse reaction, a dry ethanolic solution of ethyl o-nitrophenylpyruvate and sodium ethoxide in concentrations 0.1743 and 0.1858 M respectively was left at 76° for an extended period of time. A decrease in optical density occurred over a period of 1,300 minutes. From this time on, only a very slow decrease in absorption took place. The concentration of pyruvate in terms of optical density finally obtained in the forward reaction was 48.2 units, while that found for the reverse reaction was 41.7 units. These results are shown in Fig. 14.

It was expected that, if the reaction was in fact reversible, the same final concentration of pyruvate should occur if the initial concentration in both cases had been identical. The lower equilibrium concentration of pyruvate in the reverse reaction may be attributed in part to the slightly higher initial concentration of base used. In addition, it is possible that in both the reverse and forward reactions, minute amounts of moisture

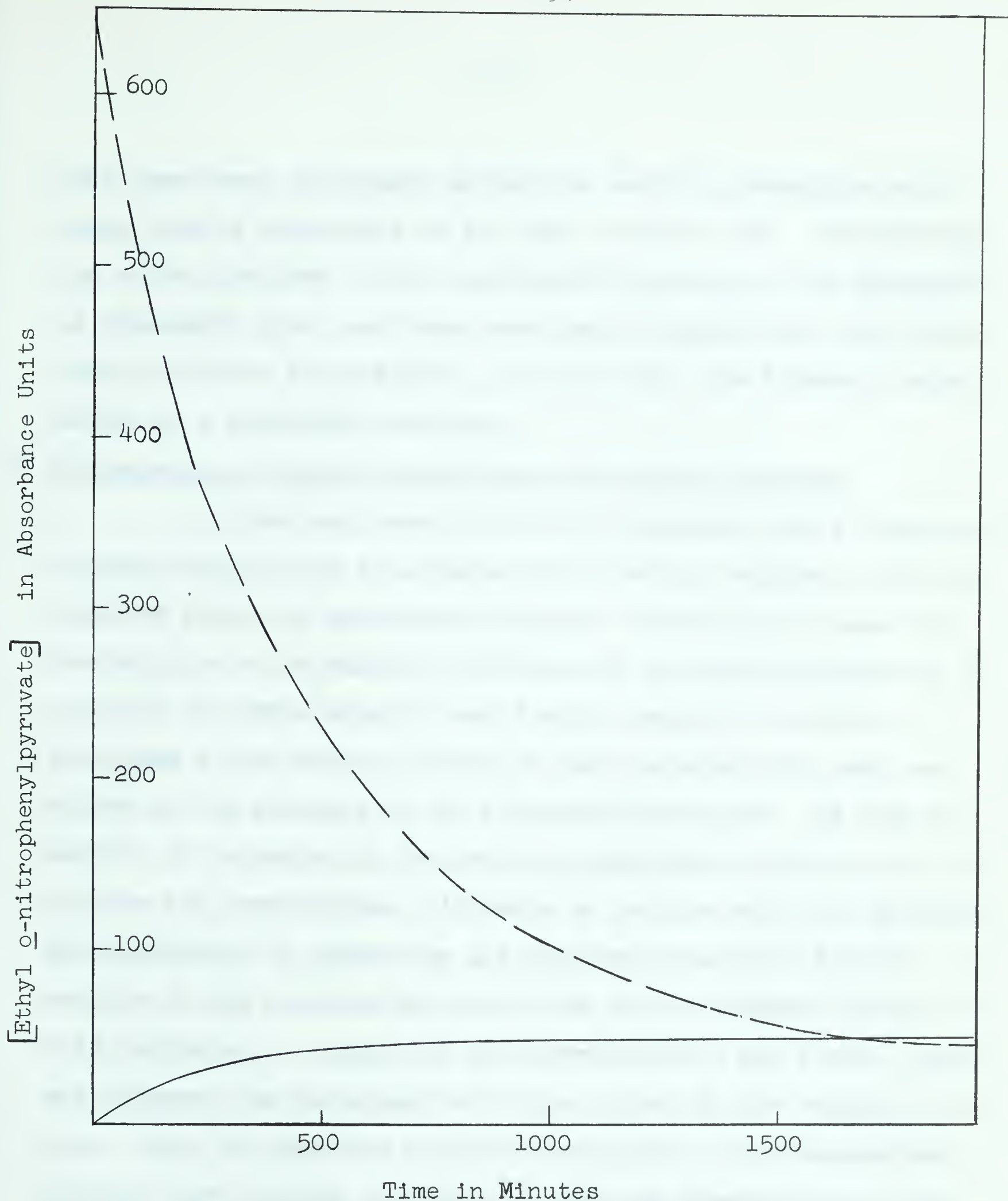


Fig. 14. Comparison of the forward (—) and reverse (---) reactions for the Reissert condensation. In the forward reaction, initial concentrations were: o-nitro-toluene, diethyl oxalate and sodium ethoxide in dry ethanol at 76°, 0.1750, 0.1750 and 0.1794 mole/liter resp. In the reverse reaction, initial concentrations were: ethyl o-nitrophenylpyruvate and sodium ethoxide in dry ethanol at 76°, 0.1743 and 0.1858 mole/liter resp.

could have been introduced during the sampling procedures which would lead to hydrolysis of the ethyl oxalate (41). Considering the errors involved in the experimental procedure, the agreement is reasonably good, and these results, in conjunction with those shown in Tables XII and XVII, indicate that the Reissert condensation is a reversible reaction.

G. Condensation of 2,4-Dinitrotoluene with Diethyl Oxalate

It has been reported in the literature that 2,4-dinitrotoluene is difficult to condense with diethyl oxalate in the presence of sodium or potassium ethoxide. Kermack (10) found that the addition of an ethanolic solution of 2,4-dinitrotoluene to a solution of sodium ethoxide and diethyl oxalate in ethanol, developed a blue colour instead of the characteristic deep red colour of the enolates of the nitrophenylpyruvates. He made no mention of isolation of the product, apparently having failed to achieve the condensation. Attempts to isolate ethyl 2,4-dinitrophenylpyruvate by condensing 2,4-dinitrotoluene with diethyl oxalate in the presence of cold dilute sodium ethoxide failed in this laboratory. Instead of the characteristic red colour, there was observed the development of a blue colour in the reaction mixture. When the solution was kept overnight at room temperature, a black tarry residue occurred. It was not possible to isolate any of the desired product from this tarry residue. However, use of a milder base, lithium ethoxide, was found to be very satisfactory in achieving the condensation, and the desired ethyl 2,4-

dinitrophenylpyruvate was isolated in very good yields, using the following procedure.

One g (0.1 mole) of clean lithium was dissolved in 100 ml of commercial absolute ethanol. When the metal was completely dissolved, 14.6 g (0.1 mole) diethyl oxalate was added and the mixture was cooled to 20° under the cold water tap. To this mixture, a solution of 9 g (0.05 mole) 2,4-dinitrotoluene in 50 ml of ethanol was added dropwise with vigorous stirring. Care was taken to see that the initial blue colour which developed on addition of the toluene solution disappeared before further addition of it. In a short time the solution became intensely red and then deposited deep red crystals. The mixture was kept overnight to complete the precipitation. The next day, 200 ml dry ether was added, and the mixture was filtered. The solid crystals were washed three times with dry ether. Deep red hygroscopic crystals were obtained (10.4 g, 72% yield). This material was immediately suspended in anhydrous ether and HCl gas bubbled until the red colour disappeared. The lithium chloride was removed by filtration and the yellow solution, upon treatment with charcoal, and reduction in volume gave 10 g of intense yellow crystals, melting at 85-86°. On purification by chromatography over silica gel with benzene-pentane mixed solvents, yellow crystals of ethyl 2,4-dinitrophenylpyruvate were obtained. M.p., 87-88°. Found: C, 47.07; H, 3.66; N, 9.81. Calc. for $C_{11}H_{10}N_2O_7$: C, 46.81; H, 3.57; N, 9.92%.

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APPENDIX I

Calculation of the Concentration of Reactants at the Reaction
Temperature

The volumes of standard stock solutions of various reactants, salts and solvents were pipetted at room temperature in the required amounts and transferred to the reaction vessel. The actual volume of the reaction mixtures at 76.3° or the other reaction temperatures were calculated, assuming it to be all ethanol (since the solutions were in relatively small concentrations) according to the equation¹

$$d_4^t = 0.80625 - 8.461 \times 10^{-4} t + 1.60 \times 10^{-7} t^2 \\ - 8.5 \times 10^{-9} t^3$$

where d_4^t = density of ethanol in gm/ml at t° C.

Substituting the proper temperature "t" in the equation the density of ethanol was calculated. From the densities at room temperature and that at the reaction temperature, the volume at the latter was obtained.

¹. International Critical Tables: McGraw-Hill Book Co., Inc., New York, 1928, Vol. III, p.27.

APPENDIX II

Rate Data for Kinetic Calculations

Table XXII

Rate Data for the Pseudo-Order Kinetic Study of o-Nitrotoluene¹

[Diethyl oxalate] = 0.376 M. [NaOC₂H₅] = 0.390 M. Ionic

strength, 0.39. Solvent, anhydrous ethanol. Reaction

temperature, 76.3°.

Molar Concentration of <u>o</u> -Nitrotoluene					
0.0083		0.0147		0.0294	
Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)
0	0.00	0	0.00	0	0.00
2	1.98	2	0.70	2	1.45
10	3.90	6	2.35	6	4.40
20	5.55	10	3.80	10	7.30
30	8.05	15	5.52	15	11.2
45	9.52	20	7.52	21	15.3
55	12.2	25	9.3	28	19.9
72	15.3	35	11.7	36	24.5
95	18.3	45	16.1	46	30.8
120	21.3	55	19.0	60	38.6
145		70	23.8	85	50.8
		85	27.0		
		100	30.7		
				0	0.00
				2	2.48
				5	6.60
				8	10.8
				12	16.6
				16	22.4
				20	27.4
				25	31.0
				30	39.4
				36	46.5
				46	53.0
				78	80.6
				0	0.00
				5	8.90
				10	16.7
				15	26.8
				20	35.0
				24	41.4
				28	49.3
				33	55.6
				40	68.2
				46	77.2

1. Data for the rate constants shown in Table V .

2. X = [ethyl o-nitrophenylpyruvate] x 10⁴.

Rate Data for the Pseudo-Order Kinetic Study of Diethyl Oxalate¹

$[\text{o-Nitrotoluene}] = 0.398 \text{ M.}$ $[\text{NaOC}_2\text{H}_5] = 0.0408 \text{ M.}$ Ionic strength, 0.408.

Solvent, anhydrous ethyl alcohol. Reaction temperature, 76.3°

Molar Concentration of Diethyl Oxalate													
0.0085		0.0170		0.0309		0.0450		0.0618		0.0927		0.124	
Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)
0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
7	0.65	2	0.92	2	1.70	2	2.30	2	3.08	2	4.80	2	11.0
16	1.70	6	1.82	5	4.15	5	5.50	5	8.15	5	12.0	7	25.2
25	2.59	10	3.20	10	6.72	10	11.10	10	15.7	10	24.4	12	37.1
35	3.42	15	5.45	16	9.55	15	15.5	15	22.9	15	34.1	15	47.2
45	4.44	20	6.98	20	12.3	20	21.6	20	29.3	20	47.1	20	61.3
60	6.11	26	9.00	24	15.2	24	26.6	25	35.6	25	57.4	25	79.1
70	6.75	35	11.5	30	19.5	30	32.4	30	49.8	30	67.5	35	102.5
85	9.14	45		37	23.8	45	40.3	40	56.1	36	79.5	45	135.0
		55		45	28.2	45	47.3	50	67.0	45	94.1		

1. Data for the rate constants shown in Table VI.

2. $X = [\text{Ethyl o-nitrophenylpyruvate}] \times 10^4$.

TABLE XXIV

Data Showing the Effect of the Changes in Ionic Strength on the Rate of Condensation of o-Nitrotoluene with Diethyl Oxalate in the Presence of Sodium Ethoxide¹

[o-Nitrotoluene] = 0.376 M. [Diethyl oxalate] = 0.376 M. Salt added, sodium iodide.

Solvent, anhydrous ethanol. Reaction temperature, $76.3 \pm 0.1^\circ$.

Time, (min)	0.0244		0.0488		0.0732	
	X ³ (M)	X ³ (M)	X ³ (M)	X ³ (M)	X ³ (M)	X ³ (M)
0	0.00	0.00	0.00	0.00	0.00	0.00
2	0.30	0.50	1.00	1.80	1.60	2.50
5	0.80	1.25	2.60	4.52	4.60	7.05
10	1.65	2.50	5.35	9.60	9.12	14.5
15	2.52	3.72	7.92	14.1	14.1	21.7
20	3.35	4.90	10.7	18.4	18.8	28.7
25		6.05	13.3	22.5	23.0	35.1
30	4.82	7.42	15.8	26.4	26.7	
35		8.28	18.1	30.2	31.5	49.6
40	6.40		20.3	33.4	34.8	
45		10.3				
50	7.78		24.1		43.00	

1. Data for the rate constants shown in Table VII.

2. Reaction rate obtained in this run was used in Table IX.

3. X = [Ethyl o-nitrophenylpyruvate] $\times 10^4$.

$$[\text{o-Nitrotoluene}] = 0.376 \text{ M.} \quad [\text{Diethyl oxalate}] = 0.376 \text{ M.} \quad [\text{Potassium ethoxide}] =$$

0.0472 M. Salt added, potassium acetate. Solvent, anhydrous ethanol. Reaction temperature $76.3 \pm 0.1^\circ$.

Ionic Strength									
0.0472 ²		0.0929		0.138		0.230		0.518	
Time (Min)	X ³ (M)	Time (Min)	X ³ (M)	Time (Min)	X ³ (M)	Time (Min)	X ³ (M)	Time (Min)	X ³ (M)
0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
4	2.99	2	1.58	2	1.65	2	1.75	2	2.32
8	6.40	5	4.12	5	4.60	5	5.15	5	6.65
13	10.2	8	7.02	8	7.55	8	8.62	10	14.1
16	12.7	12	10.5	12	11.4	12	13.1	15	20.8
20	15.7	16	13.8	16	15.1	17	19.0	20	27.2
25	19.4	20	17.2	20	18.8	22	24.1	25	33.2
30	22.8	25	20.9	25	22.9	27	28.4	30	38.9
35	26.7	30	24.6	30	27.1	34	35.3	35	44.6
40	29.6	35	28.6	35	31.2	41	41.5	40	46.8
45	32.5	40	31.5	40	35.2	47	47.2	50	59.1
		45	35.9	45	39.5				

1. Rate data for the rate constants shown in Table VIII.

2. The reaction rate obtained in this run was also used in Table IX.

3. $X = [\text{Ethyl } \underline{\text{onitrophenylpyruvate}}] \times 10^4.$

TABLE XXVI

Rate Data for the Pseudo-Order Kinetic Study of

Potassium Ethoxide¹

[Diethyl oxalate] = 0.376 M. [o-Nitrotoluene] = 0.376 M. Ionic strength maintained constant at 0.279 by addition of potassium acetate. Solvent, anhydrous ethanol. Reaction temperature, 76.3°.

Potassium Ethoxide Molar Concentration																	
0.0142			0.0236			0.0471			0.0707			0.0943			0.118		
Time (Min)	X ² (M)		Time (Min)	X ² (M)		Time (Min)	X ² (M)		Time (Min)	X ² (M)		Time (Min)	X ² (M)		Time (Min)	X ² (M)	
0	0.00		0	0.00		0	0.00		0	0.00		0	0.00		0	0.00	
5	0.41		4	1.16		2	2.06		2	3.65		2	5.12		2	8.25	
10	0.89		8	2.62		5	5.62		4	7.86		5	13.3		5	22.3	
15	1.42		12	3.40		9	10.8		8	16.1		8	21.9		8	36.5	
20	1.91		16	4.25		13	14.3		12	23.8		12	33.4		12	53.5	
25	2.40		20	5.13		18	19.8		16	31.3		16	44.6		16	72.0	
30	2.84		25	6.22		24	26.1		21	40.8		20	54.8		20	90.0	
40	3.80		30	7.22		31	32.9		27	51.7		25	68.0		25	108.0	
50	4.50		40	9.16		41	42.5		38	74.0		35	91.5				
			45	10.21		47	47.4					45	111.2				

1. Data for rate constants shown in Table X.

2. $X = [\text{Ethyl o-nitrophenylpyruvate}] \times 10^4$.

Rate Data for the Pseudo-Order Kinetic Study of Sodium Ethoxide¹

ethanol. Reaction temperature 76.3°.

1. Data for the rate constants shown in Table XI

2. $X = [\text{ethyl o-nitrophenylpyruvate}] \times 10^4.$

Rate Data for the Fourth-Order Kinetic Study of the Reissert Condensation in the

Presence of Sodium Ethoxide¹

$$[\text{O-Nitrotoluene}] = [\text{Diethyl oxalate}] = [\text{NaOC}_2\text{H}_5] = [\text{R}]. \text{ Solvent, dry ethanol.}$$

Reaction temperature, 76.3°.

Molar Concentration of the Reactant R							
0.285		0.336		0.409		0.522	
Time (min)	x^2 (M)	Time (min)	x^2 (M)	Time (min)	x^2 (M)	Time (min)	x^2 (M)
0	0.00	0	0.00	0	0.00	0	0.00
5	1.80	3	1.95	3	3.60	3	9.95
10	3.70	9	6.10	8	9.80	8	26.45
19	6.64	15	10.00	13	16.30	14	48.25
25	8.44	22	14.65	20	24.75	20	64.00
32	11.57	30	19.20	28	33.20	28	86.00
40	13.96	40	24.72	36	39.70	40	104.55
51	16.88	51	29.78	48	50.50	64	136.00
63	19.68	65	36.08	60	60.00		

1. Data for the rate constants shown in Table XIII.

2. $X = [\text{ethyl o-nitrophenylpyruvate}] \times 10^3$.

Rate Data for the Fourth-Order Kinetic Study of the Reissert Condensation in the

Presence of Potassium Ethoxide¹

$$[\text{o-Nitrotoluene}] = [\text{Diethyl oxalate}] = [\text{KOC}_2\text{H}_5] = [\text{R}]. \text{ Solvent, dry ethanol.}$$

Reaction temperature, 76.3°.

Molar Concentration of the Reactant R									
0.107		0.131		0.179		0.362		0.522	
Time (min)	x^2 (M)	Time (min)	x^2 (M)	Time (min)	x^2 (M)	Time (min)	x^2 (M)	Time (min)	x^2 (M)
0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
5	0.92	2.5	0.83	4	4.45	3	47.2	4	160.5
12	2.17	6	2.14	8	8.90	8	117.9	8	310.7
18	3.32	12	4.50	13	13.87	14	199.3	14.5	531.0
25	4.51	20	6.70	21	22.25	20	264.0	21	702.0
34	6.06	25	8.71	29	28.1	30	387.5	30	846.0
43	6.90	33	10.76	40	39.2	43	499.0	40	1029.0
52	8.35	41	13.60	51	49.9	55	582.5	50	1168.0
62	9.55	51	16.00	65	60.25	65	667.5	60	1310.0
		65	19.87						

1. Data for the rate constants expressed in Table XIII.

2. $X = [\text{ethyl o-nitrophenylpyruvate}] \times 10^4$.

TABLE XXX

Rate Data for the Comparison of Rates of Condensation of o-Nitrotoluene and p-Nitrotoluene¹

[Nitrotoluene] = [Diethyl oxalate] = [Sodium ethoxide] = 0.280 M.

Solvent, anhydrous ethanol. Reaction temperature, 76.5°.

Ionic strength = 0.28.

<u>o</u> -Nitrotoluene		<u>p</u> -Nitrotoluene	
Time (min)	X ² (M)	Time (min)	X ² (M)
0	0.00	0	0.00
5	1.80	3	1.89
10	3.70	8	5.47
19	6.63	13	8.20
25	8.43	20	13.2
32	11.5	27	17.7
40	13.9	35	22.4
51	16.9	45	27.0
63	19.7	56	32.1

¹. Rate data for Table XIV.

². $X = [\text{Ethyl } \underline{o}\text{-nitrophenylpyruvate}] \times 10^3.$

TABLE XXXI

Rate Data for the Substituent Effect on the Rate of the Reissert Condensation in

the Presence of Sodium Ethoxide¹[4-R-2-nitrotoluene] = [Diethyl oxalate] = [NaOC₂H₅] = 0.285 M. Ionic strength,

0.285. Solvent, anhydrous ethanol. Reaction temperature, 76.3°.

Substituent R									
H		F		Cl		Br		I	
Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)
0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
5	1.80	2	1.25	4	8.60	4	10.8	4	14.0
10	3.70	6	3.38	8	17.6	8	23.0	8	26.0
19	6.64	10	5.73	12	23.8	13	33.6	13	37.4
25	8.44	20	11.1	18	32.5	20	45.5	20	49.9
32	11.57	30	15.8	24	40.5	27	55.8	27	60.0
40	13.96	40	20.6	30	47.5	37	69.1	35	70.3
51	16.88	55	26.1	40	56.3	50	76.5	45	79.3
63	19.68			55	68.0			56	86.4

¹. Data used for the Hammett σ plot (ref. Table XV).². X = [ethyl 4-R-2-nitrophenylpyruvate] x 10³.

TABLE XXXII

Rate Data for the Substituent Effect on the Rate of the Reissert Condensation in the

Presence of Potassium Ethoxide¹

$$[\text{R-2-NO}_2\text{C}_6\text{H}_3\text{CH}_3] = 0.0224 \text{ M. } [\text{Diethyl oxalate}] = 0.358 \text{ M. } [\text{Potassium ethoxide}] =$$

0.403 M. Ionic strength, 0.403. Solvent, anhydrous ethanol. Reaction

temperature, $76.3 \pm 0.1^\circ$.

4-H		4-CH ₃		4-F		4-Cl		4-Br		4-I		3-Br	
Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)	Time (min)	X ² (M)
0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2	0.21	2	0.100	2	0.32	2	1.35	2	1.53	2	1.80	3	0.625
5	0.52	5	0.225	5	0.83	5	3.10	4	3.16	5	4.40	6	1.15
10	1.03	10	0.480	10	1.72	8	5.37	8	5.82	8	6.89	10	1.72
15	1.57	15	0.655	15	2.48	12	7.38	12	8.23	13	10.9	18	2.51
20	2.09	20	0.945	20	3.22	16	9.28	16	10.4	18	12.6	26	2.98
25	2.51	25	1.11	25	3.88	20	10.8	20	12.8	24	14.7	35	3.30
30	2.97	30	1.35	30	4.55	26	13.9	25	13.5	30	16.3	50	3.75
35	3.40	35	1.56	35	5.31	32	15.5	30	14.8	36	17.4	65	4.00
40	3.77	40	1.77	41	5.78	35		35	15.7				

1. Data used for the Hammett σ plot. (ref. Table XVI).2. $X = [\text{Ethyl R-2-nitrophenylpyruvate}] \times 10^3$.

Rate Data for the Solvent Effect on the Rate of the Reissert Condensation¹

Ionic strength, 0.1039. Reaction temperature, as shown in Table XVII. Solvent used, Benzene-ethanol mixtures.

Ratio of Benzene : ethanol, (vol/vol) _____											
0:100		30:70		70:30		80:20		90:10		100:0	
Time (min)	x^2 (M)	Time (min)	x^2 (M)	Time (min)	x^2 (M)	Time (min)	x^2 (M)	Time (min)	x^2 (M)	Time (min)	x^2 (M)
0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2.5	0.86	5	1.10	2	0.80	5	2.80	2	1.40	2	22.7
10	1.55	10	1.80	8	2.15	10	4.58	6	4.10	5	54.3
21	2.66	15	2.60	16	3.90	16	7.45	10	7.50	10	82.5
41	4.40	20	3.30	25	5.80	23	10.2	14	9.30	15	96.5
60	6.10			35	8.05	29	12.9	20	12.4	25	105.0
		35	5.60	45	10.5	35	15.2	25	15.0		
		45	7.00	35	11.9	42	18.2	30	17.9		
		56	8.60					35	21.1		
								40	26.9		
								51	30.0		

2. $X = [\text{Ethyl o-nitrophenylpyruvate}] \times 10^4$

Data for the Temperature Coefficient of the Rate of the Reissert Condensation¹

Solvent, anhydrous ethanol. Ionic strength ≈ 0.4 .

Reaction temp.	76.3°	53.6°	35.1°
[<u>o</u> -Nitrotoluene] (M)	0.0588	0.0604	0.0619
[Diethyl oxalate] (M)	0.376	0.386	0.396
[Sodium ethoxide] (M)	0.390	0.402	0.412
	Time (min) X² (M)	Time (min) X² (M)	Time (min) X² (M)
	00.00 22.48 56.60 810.8 1216.6 1622.4 2531.0 3039.4 3646.4 4653.0	00.00 30.98 102.48 184.25 255.80 317.30 4911.7 5612.7	00.00 50.300 100.550 200.700 301.10 401.40 602.00 712.65

1. Data for Table XVIII.

2. $X = [\text{Ethyl } \textit{o}\text{-nitrophenylpyruvate}] \times 10^4$.

TABLE XXXV

Rate Data for the Forward and Reverse Reactions of the Reissert
Condensation¹

Solvent, anhydrous ethanol. Reaction temperature, 76.3°

Forward Reaction		Reverse Reaction	
[o-Nitrotoluene] = 0.175 M		[Ethyl o-nitrophenylpyruvate] = 0.174 M	
[Diethyl oxalate] = 0.175 M		[Sodium ethoxide] = 0.156 M	
[Sodium Ethoxide] = 0.179 M			
Time (min)	X ²	Time (min)	X ²
0	0.00	0	650
9	1.68	8	628
17	3.08	20	622
35	6.10	30	610
56	9.35	40	594
78	12.70	57	581
95	14.9	77	513
123	18.3	104	468
249	31.5	161	416
290	34.3	241	322
345	38.0	310	263
505	45.0	375	225
572	46.0	521	163
690	46.5	580	150
800	46.8	683	115
950	47.4	764	107
1080	48.0	823	91.3
1110	48.3	1305	41.5
1215	48.3	1380	41.6
1275	48.3	1450	40.0

1. Data for Figure 14.

2. X = [Ethyl o-nitrophenylpyruvate] in absorbance units.

TABLE XXXVI

A Sample Calculation of the Pseudo-First-Order Rate Constants
of o-Nitrotoluene

[Diethyl oxalate] = 0.376 M. [NaOC₂H₅] = 0.376 M.
[o-Nitrotoluene] = 0.0147 M. Ionic strength, 0.376. Solvent,
dry ethanol. Reaction temperature, 76.3°.

Time (min)	Absorbance	Dilution factor	x ¹ (M)	(a-x) ² (M)	log(a-x) ³
0	0.000	5	0.000000	0.01470	2.1673
6	0.169	5	0.000235	0.01446	2.1604
10	0.275	5	0.000380	0.01432	2.1560
15	0.400	5	0.000552	0.01415	2.1507
20	0.545	5	0.000752	0.01395	2.1446
25	0.671	5	0.000930	0.01377	2.1391
35	0.915	5	0.001167	0.01353	2.1315
45	1.165	5	0.001612	0.01309	2.1168
55	0.683	10	0.001895	0.01280	2.1075
70	0.859	10	0.002380	0.01232	2.0907
85	0.978	10	0.002700	0.01200	2.0793
100	1.109	10	0.003070	0.01163	2.0657
115	1.229	10	0.003400	0.01130	2.0532
135	1.358	10	0.003760	0.01094	2.0392
155	1.499	10	0.004290	0.01041	2.0174

¹ x = [Ethyl o-nitrophenylpyruvate].

² a = [o-Nitrotoluene].

³ A plot of log(a-x) versus time is shown in Figure 15. The rate constant was determined by multiplying the slope of the best straight line obtained for the initial points by 2.303. The influence of the reverse reaction is clearly illustrated by the increasing deviation of the points from the straight line as the reaction proceeds.

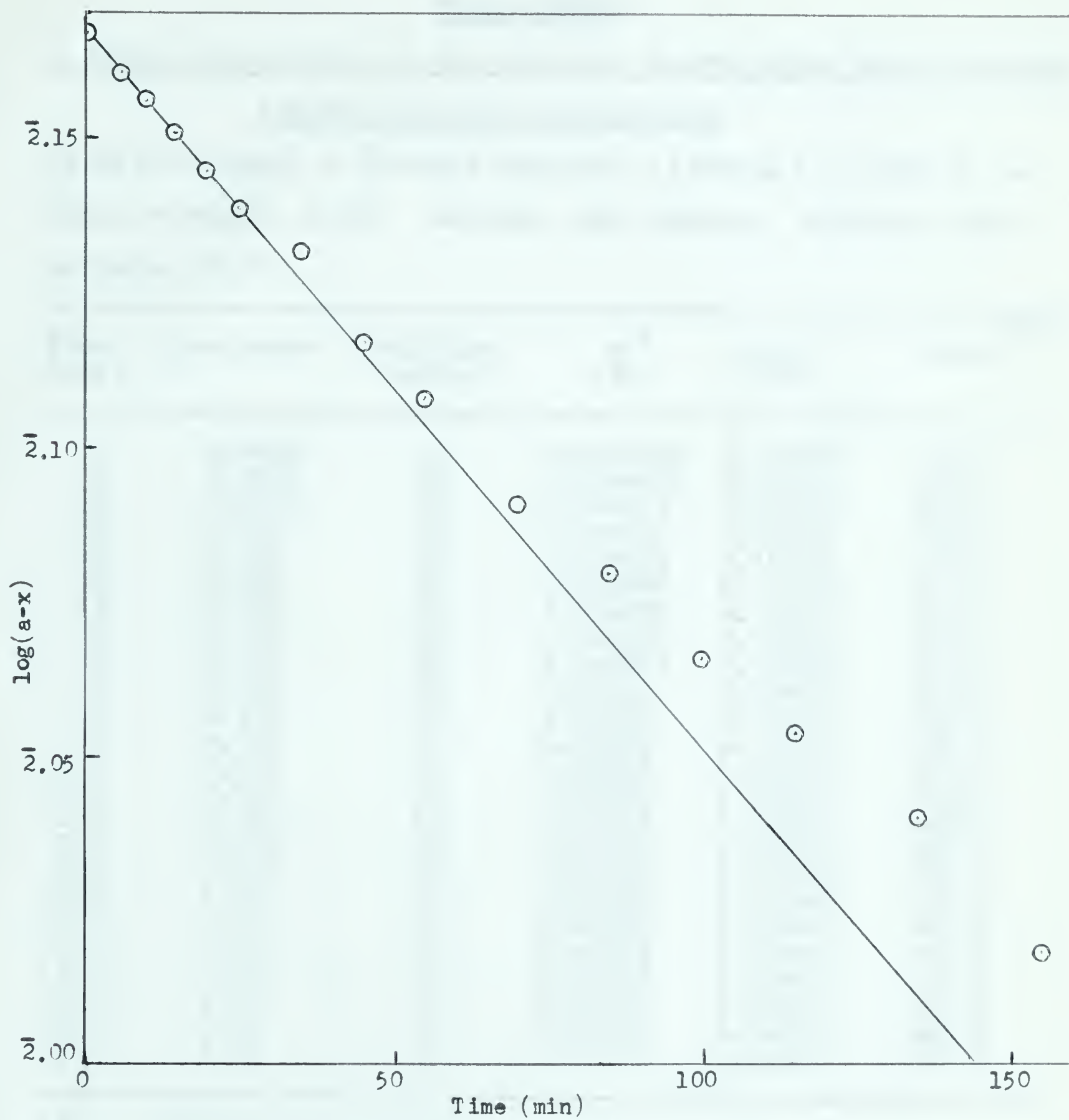


Fig. 15. A pseudo-first-order plot for *o*-nitrotoluene from the data in Table XXXVI.

TABLE XXXVII

A Sample Calculation of the Over-all Fourth-Order Rate Constants
for the Reissert Condensation

$[\text{o-Nitrotoluene}] = [\text{Diethyl oxalate}] = [\text{KOC}_2\text{H}_5] = 0.107 \text{ M} = a.$
Ionic strength, 0.107. Solvent, dry ethanol. Reaction temperature, 76.3°.

Time (min)	Absorbance	Dilution factor	x^* (M)	(a-x) (M)	$(a-x)^{-3**}$
0	0.0000	10	0.0000000	0.10780	797.6
5	0.0341	10	0.0000920	0.10774	799.6
12	0.0810	10	0.000217	0.10762	802.3
18	0.124	10	0.000332	0.10750	805.0
25	0.168	10	0.000451	0.10738	807.7
34	0.226	10	0.000606	0.10723	811.0
43	0.255	10	0.000690	0.10714	813.1
52	0.310	10	0.000835	0.10699	816.4
62	0.355	10	0.000955	0.10688	819.0
73	0.410	10	0.00110	0.10672	822.6
85	0.470	10	0.00126	0.10657	826.2
94	0.515	10	0.00139	0.10644	829.2
112	0.600	10	0.00165	0.10622	834.4
133	0.685	10	0.00184	0.10599	839.9
166	0.796	10	0.00213	0.10570	846.8
186	0.850	10	0.00227	0.10555	850.4
223	0.955	10	0.00255	0.10528	856.9
262	1.04	10	0.00278	0.10505	862.6
302	1.13	10	0.00302	0.10484	867.8
353	1.19	10	0.00318	0.10465	872.5
446	1.28	10	0.00342	0.10440	878.8
512	1.33	10	0.00356	0.10427	881.9
608	1.35	10	0.00361	0.10422	883.3
784	1.41	10	0.00377	0.10406	887.2

* $x = [\text{Ethyl o-nitrophenylpyruvate}]$.

** A plot of $(a-x)^{-3}$ versus time is shown in Figure 16. The rate constants were determined by dividing the slope of the straight line through the initial points by 3. The influence of the reverse reaction is clearly indicated by the deviation of the points from the straight line as the reaction proceeds.

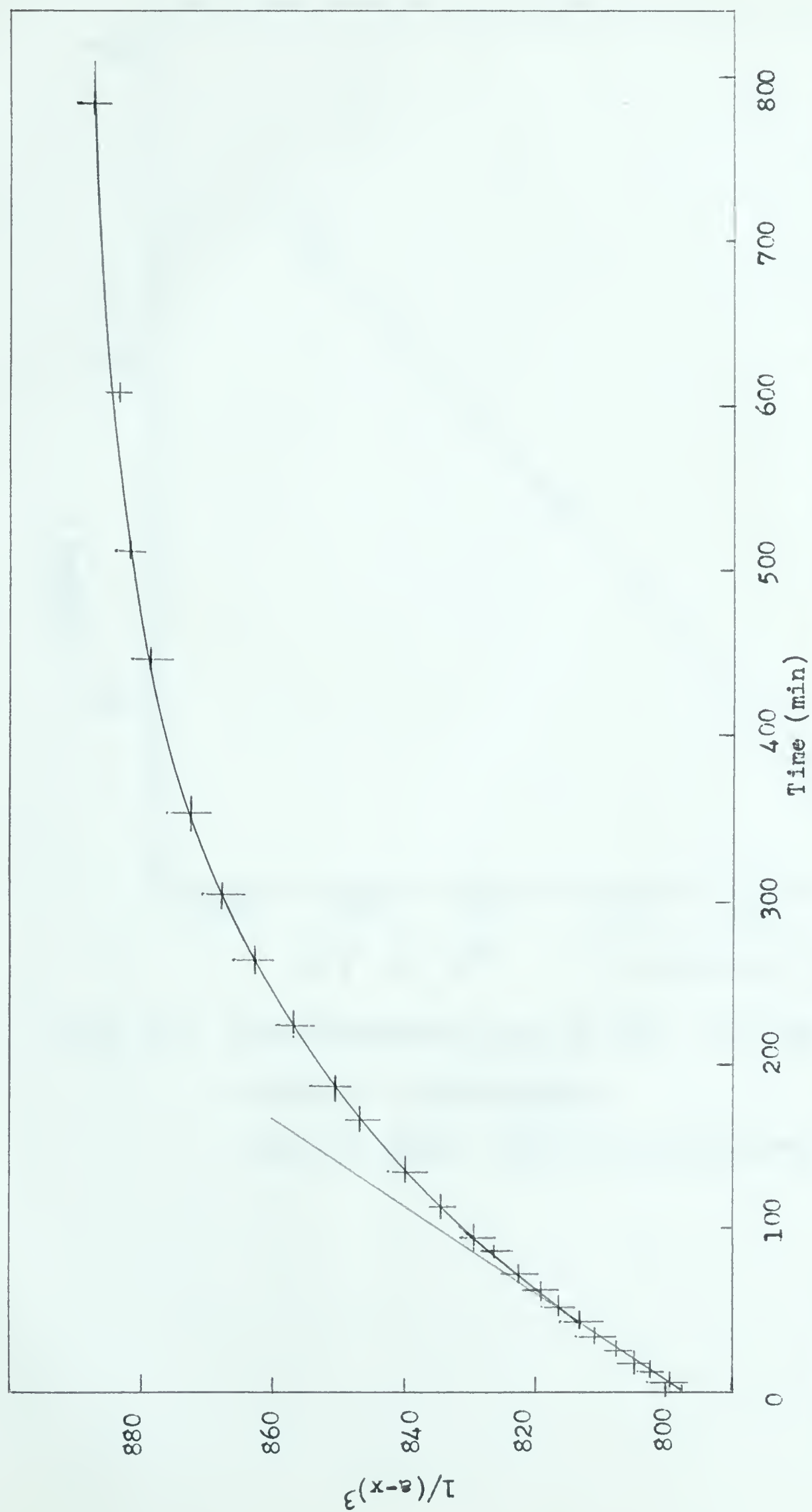


Fig. 16. $\ln$ over-all fourth-order plot for the Reissert condensation reaction from the data in

Table XXXVII.

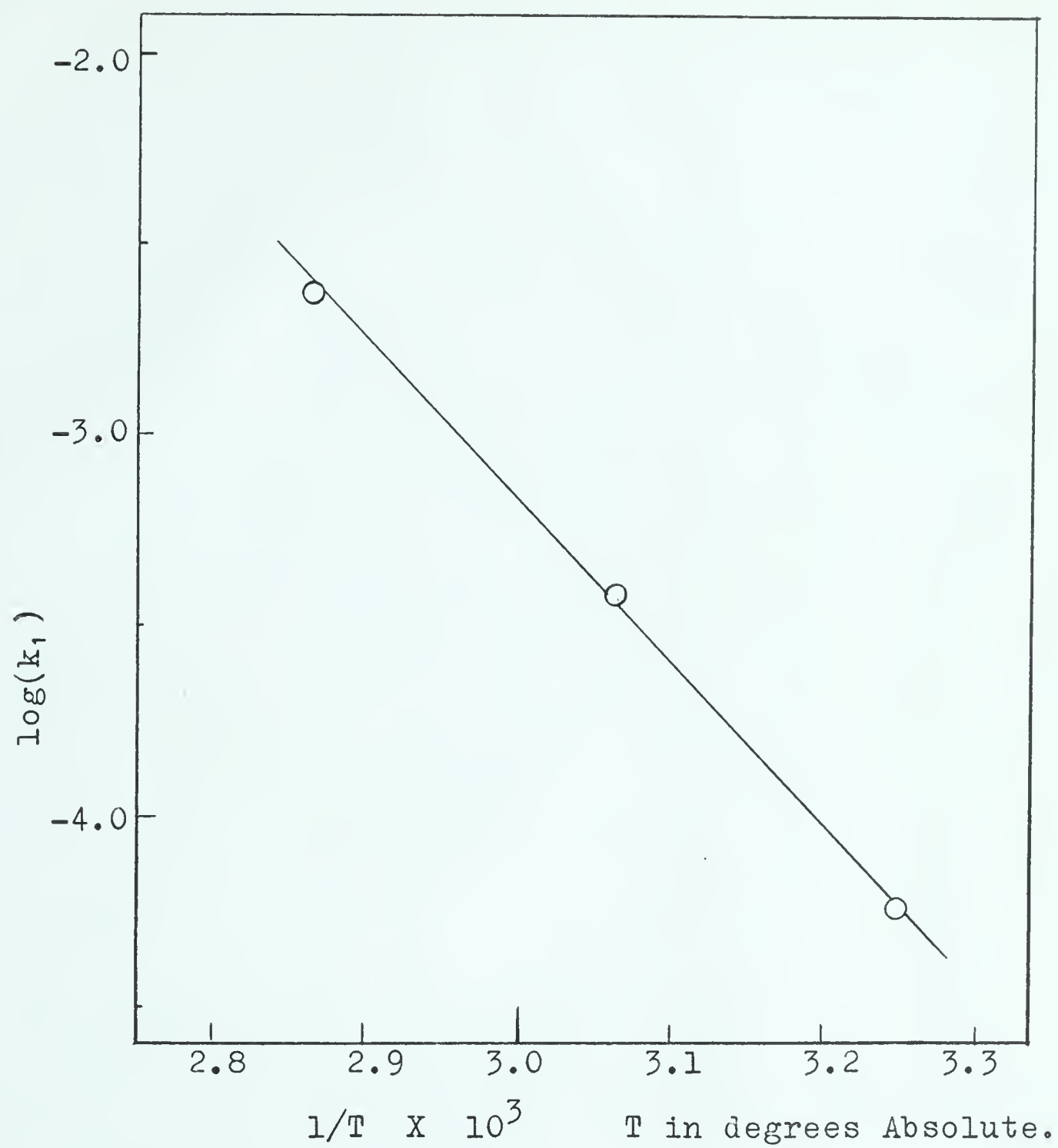


Fig. 17. The Arrhenius plot of $1/T$ vs. $\log(k_1)$ for the Reissert condensation.

Data in Table XVIII has been used for the plot.

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